Exploitation of macrocyclic chemical space by multicomponent reaction (MCR) and their applications in medicinal chemistry

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Chapter 2

Two-Step Synthesis of Complex Artificial Macrocyclic Compounds

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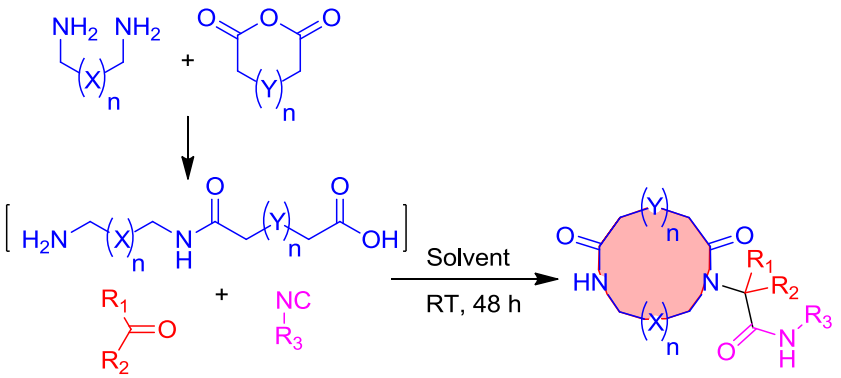


Abstract

The design and synthesis of head-to-tail linked artificial macrocycles using the Ugi reaction has been developed. This synthetic approach of just two steps is unprecedented, short, efficient and works over a wide range of medium (8-11) and macrocyclic (≥12) loop sizes. The substrate scope and functional group tolerance is exceptional. Using this approach, we have synthesized 39 novel macrocycles by two or even one single synthetic operation. The properties of our macrocycles are discussed with respect to their potential to bind to biological targets that are not druggable by conventional, drug-like compounds. As an application of these artificial macrocycles we highlight potent p53-MDM2 antagonism.

Introduction

Artificial non-peptide-derived macrocycles are a rather rare and neglected compound class, presumably owing to their complex sequential synthesis.[1] Moreover, they have generally not been classified as orally bioavailable and drug-like, until recent advancements in their synthesis and development.[2] However, macrocycles have huge potential in targeting modern postgenomic targets that are difficult to address by small molecules, such as protein–protein interactions (PPI) which are currently a therapeutic domain mostly covered by antibodies.[3-5] As opposed to their natural counterparts, artificial macrocycles promise to provide better control over synthesizability and physicochemical properties, thereby resulting in drug-like properties. However, very few synthetic methods allow convergent and fast access to a large macrocyclic chemical space, without jeopardizing chemical diversity.[6-10]

Owing to increasing interest in macrocycles, many efforts have been made to identify new synthetic methods for their preparation.[11-12] To date, the majority of these methods have focused on sequential multistep peptide synthesis, followed by stapling, for example, through disulfide bridges, cysteine-based cross linkers, RCM, or click chemistry.[13] These strategies are not suitable for the elaboration of medium-sized rings or macrocycles with non-natural (non amino acid) side chains and additional ring heteroatoms. Therefore, we introduce herein a general synthesis concept for the fast assembly of macrocycles of different size and shape, side-chains and functional-group content. We envisioned a linker moiety that makes use a simple and versatile chemistry. The linker moiety is decorated with orthogonal α,ω-functional groups that can be macrocyclized by another diverse chemistry. Recently, we published an example of this general concept, where we synthesized the linker motif by employing Ugi tetrazole chemistry, followed by a macrocyclization using a second Passerini or Ugi multicomponent reaction (MCR).[14-15]

Herein, we wanted to create a manifold of artificial macrocycles through an even shorter sequence involving an initial linear diversification, followed by an exponential diversification step of macrocyclization using Ugi MCR, thereby resulting in an overall 2-step synthesis of complex macrocycles (**Figure 1**, **Scheme 1**).

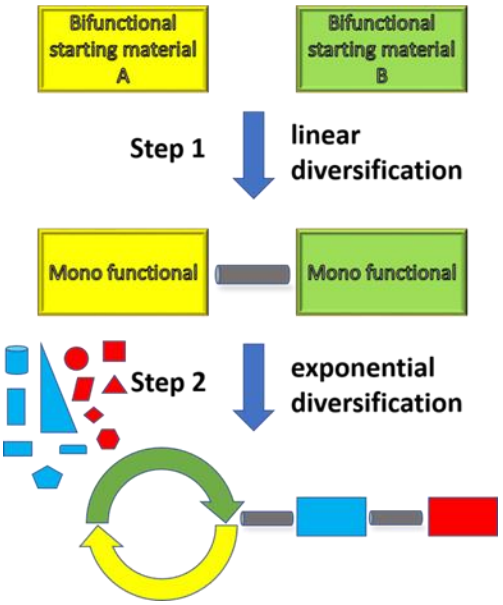
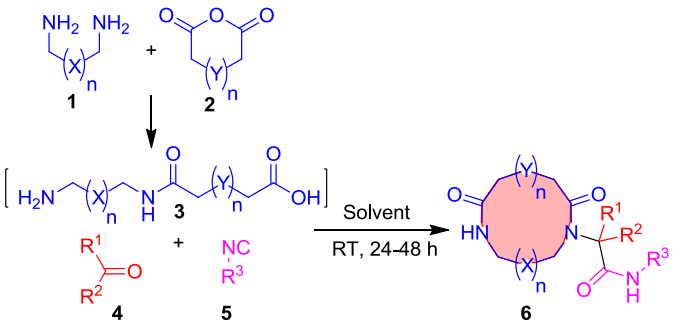


Figure 1. Synthetic concept of rapid generation of macrocycles.



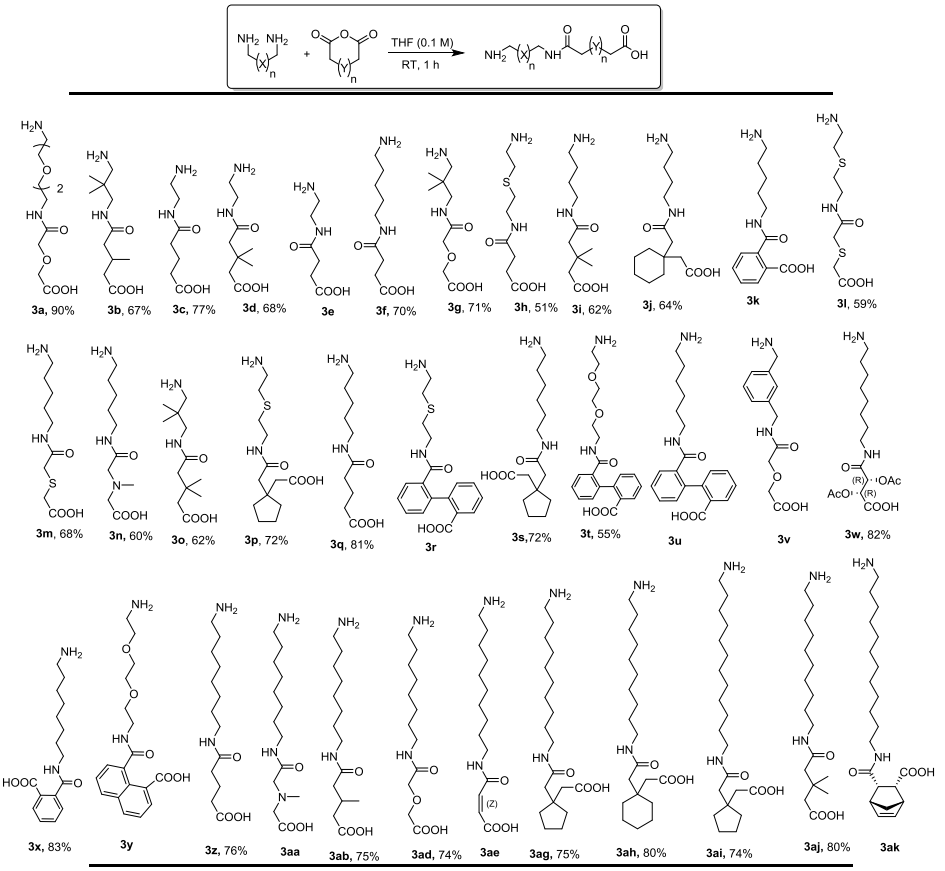
Scheme 1. Direct 2-step macrocyclization.

Results and Discussion

A core feature of our strategy was the use of simple, predictable reactions between diamines, cyclic anhydrides, aldehydes and isocyanides, all of which are starting materials that are widely available. The first step involved the ring opening of cyclic carboxylic acid anhydrides with symmetrical diamines to yield α,ω-amino carboxylic acids. For unambiguous reactivity, we first reacted the mono-Boc-protected diamines to yield α,ω-N-Boc amino carboxylic acids, however we soon abandoned this strategy. In order to introduce more flexibility, avoid the use of the halogenated solvent $CHCl_3$, and reduce the number of steps, we envisioned performing the direct ring-opening reaction of cyclic anhydrides with unprotected alkyl diamines. To this end, we synthesized a 36-membered

library of terminal amino acids of different chain lengths through the ring opening reaction from commercially available alkyl diamines and cyclic anhydrides in good to excellent yields (**Table 1**).

Table 1. Synthesized examples of α,ω-amino acids with yields. The amino acids **3e**, **3k**, **3r**, **3u**, **3v**, **3y**, **3aa**, **3ae** and **3ak** were not isolated but used directly in the following ring closure reaction.[a]



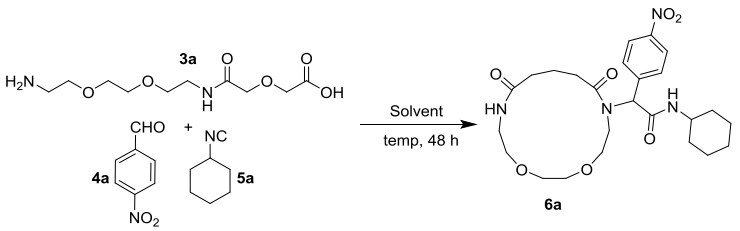
[a] Yield refers to the column-purified products.

Next, we optimized the conditions for the Ugi ring-closure of macrocycles (**Table 2**). The optimized conditions were 1.0 equiv. of amino acid **3**, 1.0 equiv. of aldehyde/ketone **4**, 1.0 equiv. of isocyanide **5** in 0.01M solution of MeOH at room temperature for 24 to 48 h. 14-amino-5-oxo-3,9,12-trioxa-6-azatetradecan-1-oic acid **3a** together with 4-nitrobenzaldehyde and cyclohexyl isocyanide was investigated as our model system.

The Ugi-reaction with 4-nitrobenzaldehyde and cyclohexylisocyanide in 1.0 M solution of MeOH after 48h furnished the expected 15-membered macrocycle **6a** in 30% yield without any oligomerization byproducts. Nonpolar and polar aprotic solvents did not produce any product at all due to the low starting material solubility. Moreover, these are

uncommon solvents for the Ugi reaction which is best performed in protic polar solvent. The same reaction was performed in different dilutions of methanol and it was found that highly dilute 0.01M equimolar mixture gave the 15-membered macrocycle **6a** in good yield (55%). Although trifluoroethanol (57% yield) was slightly superior to MeOH we chose MeOH for further scope and limitation studies due to the higher pricing of TFE.

Table 2. Optimization Conditions for the Synthesis of Macrocycles.



	Solvent (M)	Temp.	Yield (%)[a]
1	MeOH (1.0 M)	RT	30
2	MeOH (0.25 M)	RT	30
3	MeOH (0.1 M)	RT	38
4	MeOH (0.02 M)	RT	47
5	**MeOH (0.01 M)**	**RT**	**55**
6	MeOH:H_2O (0.01 M) (3:1)	RT	33
7	MeOH (0.01 M)	60 °C	48
8	**TFE (0.01 M)**	**RT**	**57**
9	Glycerol:MEG (0.01M) (3:1)	RT	21

[a] Yield refers to the column-purified products. MEG = Monoethylene Glycol

With this optimized condition in hand, we studied the scope of macrocyclization. We synthesized a small library of 39, 8- to 19-membered medium to macrocycles in 22 to 75% yields (**Table 3**, **Scheme 2** and **6ad**). Different lengths of terminal amino acids, including simple methyl chains, heteroatoms, small rings, and periphedral groups, furnished the macrocycles in good yields. Heteroatoms in a ring, for example, N-methylated macrocycles, are interesting because they can increase hydrophilicity. Phenyl, potentially

atropisomeric biphenyl, and naphthyl moieties can be conveniently included as ring fragments.

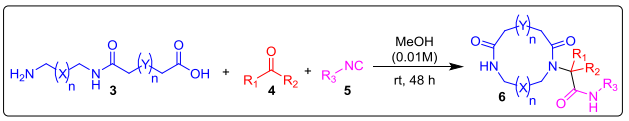
Unprotected orthogonally functionalized oxo components such as 3-hydroxybenzaldehyde, terephthalaldehyde and 2-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)acetaldehyde were tolerated under the reaction conditions and furnished the target macrocycles (**6l**, **6s** and **6ai**) in 72%, 43% and 29% yields, respectively. These functional groups can be potentially be further elaborated into different products. Similarly, to aldehydes, ketones also worked well and could be incorporated as side chains of different macrocycles in good to excellent yields.

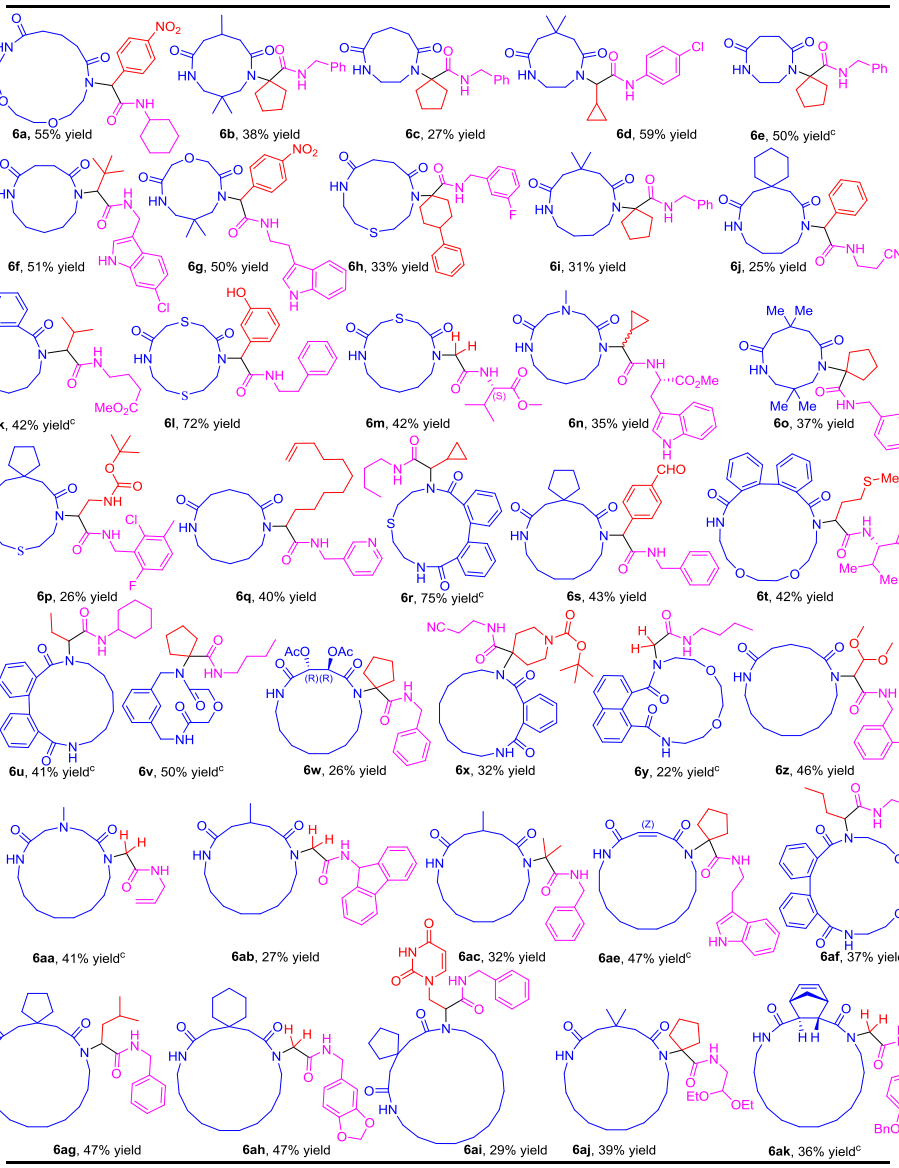
The universality of this macrocyclization reaction was further supported by using various functionalized isocyanides derived from aliphatic, aromatic, benzylic, amino acid and heterocyclic compounds. Fascinatingly, all these isocyanides reacted very smoothly and resulted in a variety of macrocycles in good yields. The ability of the designed macrocyclization to address complexity was assessed by using tylosin as an oxo component.

We synthesized the tylosin based macrocycle **6al** in good yield (53%) with 8:1 ratio of diastereomers that were separated by chromatography. This example nicely underscores the mildness of the procedure which was shown to be compatible with free hydroxyl groups, α,β-unsaturated ketones, esters, and acetals. Another complex macrocycle is **6am**, which can be accessed in just two steps based on a glycosyl isocyanide.[16] Chirality control was introduced in macrocycle **6w**, which is derived from tartaric acid. Our examples indicate that more elaborated substitution patterns and chiral centers can also be employed and lead to complex macrocycles that are valuable and otherwise difficult to prepare, including spirocycles and phenyl, biphenyl, naphthyl, pyridine-containing, tylosin-derived, and glycosylated macrocycles

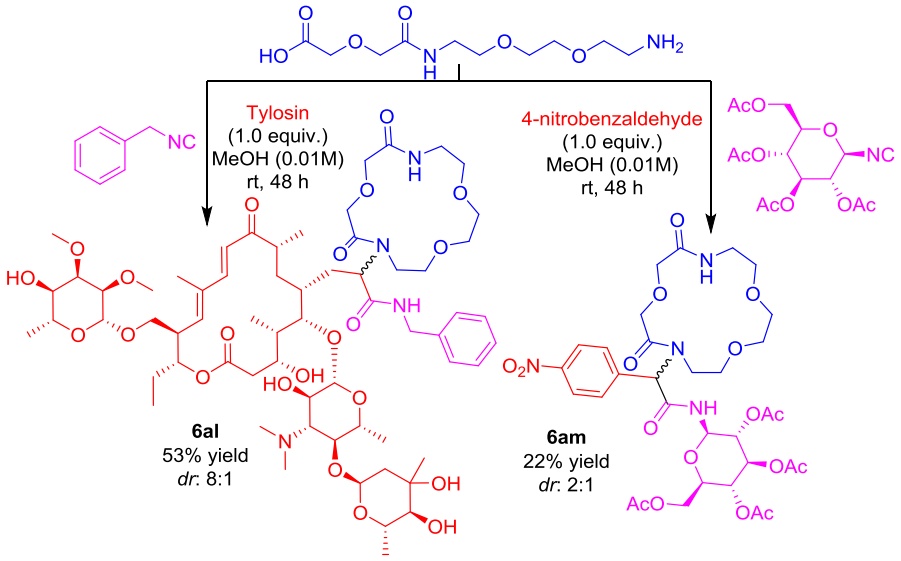
In some cases, we faced problems in isolating the α,ω-amino acids owing to their high polarity (**Table 1**, **3e**, **3k**, **3r**, **3u**, **3v**, **3y**, **3aa**, **3ae** and **3ak**). In these cases, we removed the THF solvent from the anhydride ring-opening reaction and reacted the crude α,ω-amino acids with the oxo and isocyanide components in the Ugi reaction. Surprisingly, the one-pot reaction also produced the desired products (**6e**, **6k**, **6r**, **6u**, **6v**, **6y**, **6aa**, **6ae** and **6ak**) in good to moderate yields (**Table 3**).

Table 3. Substrate scope of the macrocyclization.[a,b]





[a] Unless otherwise noted, the reaction was conducted with 1.0 mmol of amino acid, 1.0 mmol of aldehyde/ketone and 1.0 mmol of isocyanide in MeOH (0.01 M) for 24-48 h at rt. [b]Yield refers to the column-purified products. [c]Reaction performed in a cascade one-pot manner (ring opening followed by macrocyclization)



Scheme 2. Synthesis of Tylosin and sugar-based macrocycles (**6al** and **6am**).

For a number of the macrocycles we were able to grow crystals and solve the 3D structures. Interestingly in several of the structures, the exocyclic amide group is bent back over the macrocycle to form an intramolecular hydrogen bond with the macrocycles amide group (**Figure 2**). It has been shown that similar exocyclic amide-group arrangements provide structural rigidity within cyclic peptidomimetics and promote the creation of a stabilizing intramolecular hydrogen-bonding network.[17] This exocyclic control element can also contribute to increased membrane permeability by allowing the macrocycles to switch between membrane and aqueous-solution-optimized conformations in a manner reminiscent of a chameleonic behavior.[18] Thus, intramolecular hydrogen bonds can contribute to the flexibility of the macrocycles to allows them to adapt to their environment, thereby combining aqueous and lipid solubility, cell permeability, and efficient target binding.[19]

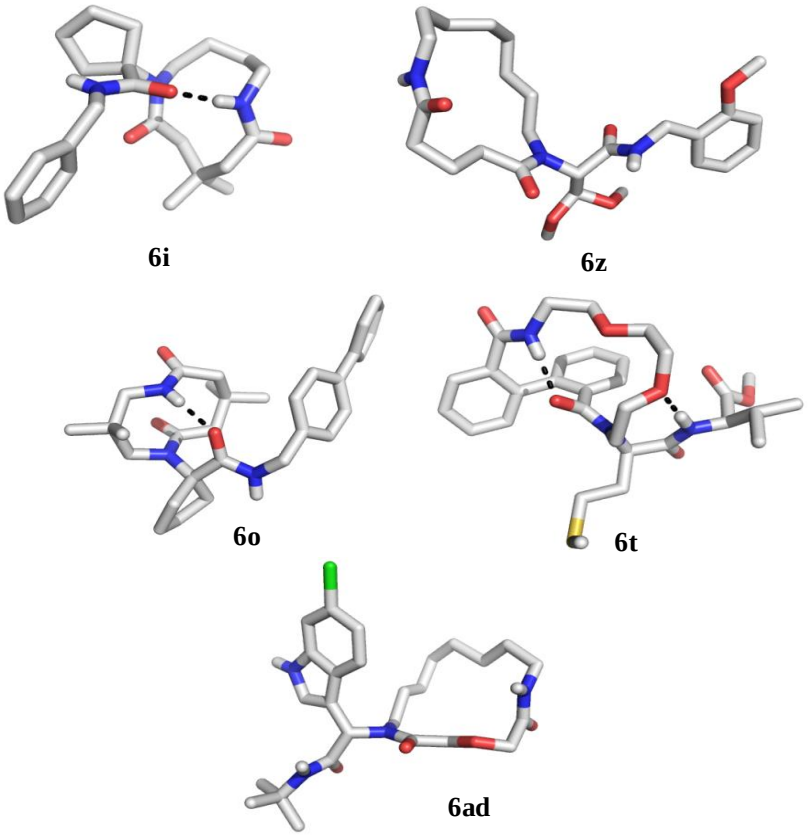


Figure 2. 3D structures and intramolecular hydrogen bonding of several macrocycles **6i**, **6o**, **6t**, **6z** and **6ad** as indicated by black dotted lines.

Whitty and co-workers recently analyzed multiple X-ray structures of natural-product macrocycles in their protein receptors and proposed specific guidelines for the design of synthetic macrocycle libraries with structural and physicochemical features likely to favor strong binding to protein targets as well as good bioavailability.[20] Thus, we compared the calculated values based on the 38 herein described artificial macrocycles with Whitty's dataset (**Table 4**). Macrocyclic groups based on heavy atoms (HA) were categorized as (i) 'ring atoms', (ii) 'peripheral atoms', that is, small groups such as methyl, carbonyl, hydroxyl and halogen moieties that consist of a single HA appending the ring, and (iii) 'substituent atoms', comprising larger structures connected to the ring. Structural diversity of all three regions is important for binding to the receptor. All the regions of our artificial macrocycles are within or close to the range of Whitty's design rules. The balance of polar to non-polar atoms that is important to ensure adequate polar surface area (PSA) is critical for good aqueous solubility. cLogP, MW and other parameters also compare favorably with

the dataset of Whitty (**Table 5**, **Figure 3**). In summary, our artificial macrocycles fall well into Whitty's design criteria for macrocyclic libraries in most properties.

Table 4. Comparison of the Whitty criteria of 38 randomly selected artificial macrocycles (**6a-6ak** and **6am**) with the Whitty dataset of 19 natural product macrocycles. Green filling denotes criteria overlap whereas yellow filling closeness to the criterion.

Property	Observed range (Whitty)	Our MC in range
Ring size (*R*)	14–38	8-19
Number of substituents	4.4 (3–8)	1-3
Large substituents (≥5 HA)**b**	1.9 (1–3)	1-3
Small substituents (2–4 HA)**b**	2.4 (1–6)	0-1
Proportion of HA that are in substituents	47% (40–59%)	53% (32-81%)
Number of peripheral groups	5–12	2-5
Polar/nonpolar balance, substituents	~30/70	~35/65
Polar/nonpolar balance, peripheral groups	~60/40	70/30
Degrees of unsaturation in ring	~0.4R – 4 (± 3)	~0.5R–4(±4)
N:O ratio	0.25:1 (0–0.4:1)	0.75:1
Chiral centers	15 (9–18)	0-6

Table 5. MW, cLogP, PSA, HBDs, HBAs and N_{RB}value comparative table**:** the dataset of Whitty´s 19 unique MCs and our 38 MCs (**6a-6ak** and **6am**).

Property[a]	Whitty 19 MCs (*avg*)	Our 38 MCs (*avg*)
MW	778	491
clogP	2.73	2.61
PSA[b]	210 Å2	102 Å2
HBDs[c]	4.8	2.2
HBAs[d]	10.6	4.3
N_{RB}value	8.7	6.0

[a]Calculatorplug-ins (Instant J Chem version 16.5.2.0) were used for structure property prediction and average values are presented here. [b]Polar surface area. [c]Number of hydrogen bond donors. [d]Number of hydrogen bond acceptors.

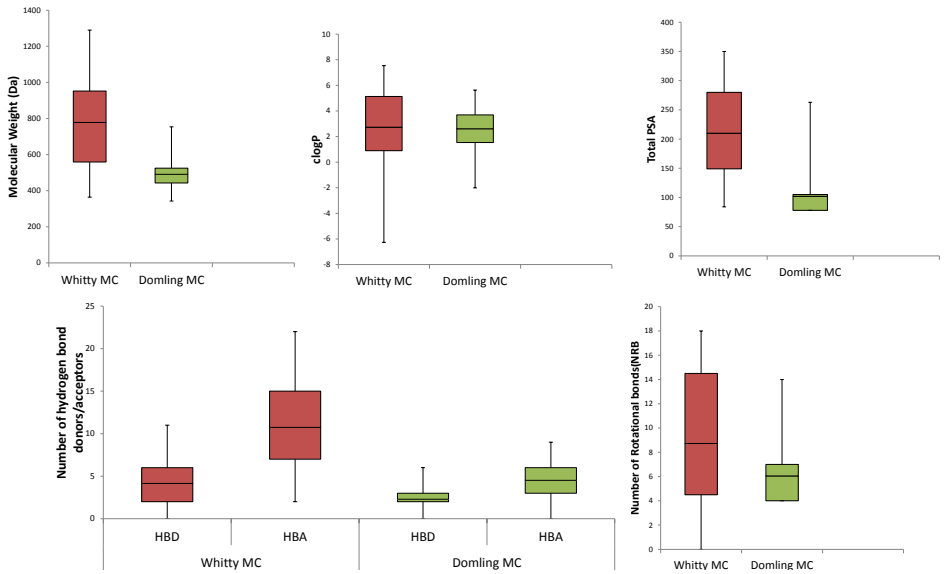


Figure 3. MW, cLogP, PSA, HBDs, HBAs and N_{RB} value whisker plots: The dataset of Whitty´s 19 unique MCs and our 38 MCs (**6a-6ak** and **6am**). Different properties of dataset and mean values were calculated by using Instant JChem (version 16.5.2.0). Whitty´s 19 macrocycles included in the test set are Cyclosporin, Sanglifehrin A, Rapamycin, FK506, Scyptolin, GE2270A, Nodularin R, Arylomycin, Argadin, Argifin, Pectenotoxin-2, Kabiramide C, Reidispongiolide A, Latrunculin B, Soraphen A, Geldanamycin, Pochoxime A, Macbecin, Radicicol and the properties are compared with our 38 MCs **6a-6ak** and **6am**.

Macrocycles possess a larger surface area than small molecules and have been proposed to be a suitable molecular class to antagonize protein-protein interactions (PPIs). Specifically, loops and their binding partners represent new and promising PPIs for the development of macrocycle and constrained peptide inhibitors.[21] Based on our previous knowledge of p53-MDM2 antagonists and as an application of our macrocycles we have designed 15-membered molecule **6ad** which should mimic the hot-spot triad (F19, W23 and L26) of p53 interacting with the negative regulator protein MDM2 (**Figure 4**).[22]

We tested the binding of **6ad** towards MDM2 by 2D HSQC-NMR and fluorescence polarization and found a binding constant K_i of 2.25 μM (Table 6). In accordance with the peak shifts of MDMD2 and the modelling we speculate that the macrocycles binds into the L26 pocket, the 6-chloro indole moiety into the W23 and the tert-butyl group into the F19 pocket of the triad binding site. To the best of our knowledge this is the first artificial macrocycle shown to bind to the MDM2 receptor. Stapled peptides bind also to MDM2 but their staple is oriented to a binding site adjacent to the hot-spot.[23] Future reporting will be done on detailed SAR of artificial macrocycles binding to MDM2 and other protein-protein interactions.

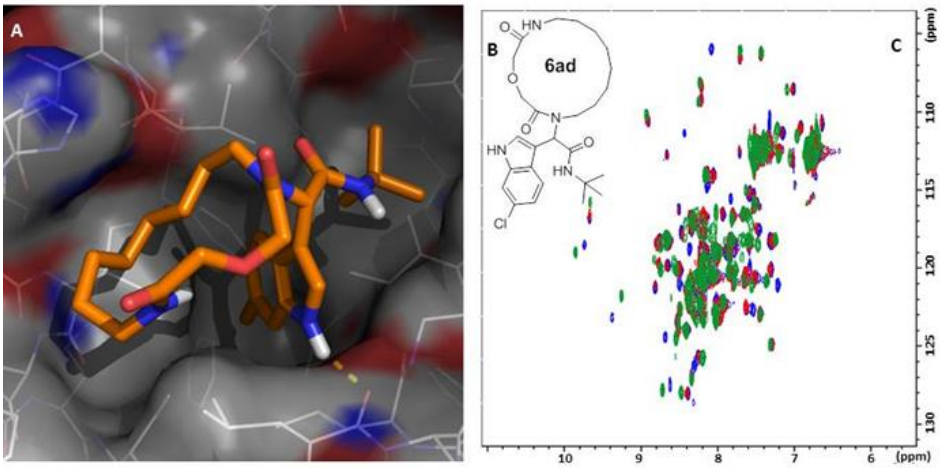
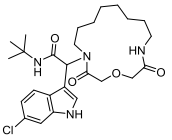
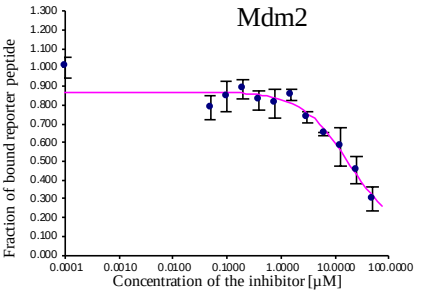


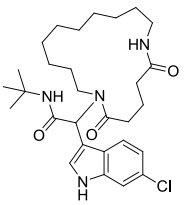
Figure 4. Macrocycle **6ad** binding to MDM2 receptor **A**: Modelling of **6ad** into MDM2 receptor (PDB ID 1YCR); **B**: Superimposed ^{1}H-^{15}N HSQC NMR spectra ^{15}N-labelled MDM2 titrated with 6ad: blue-reference MDM2 spectrum, red–4:1 (MDM2:6ad) titration step, green–1:5 (MDM2:6ad; overtitration); **C**: 2D structure of **6ad**.

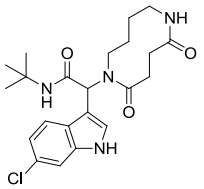
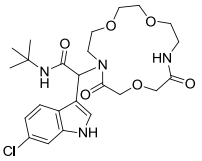
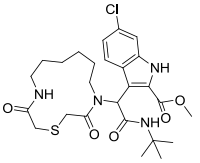
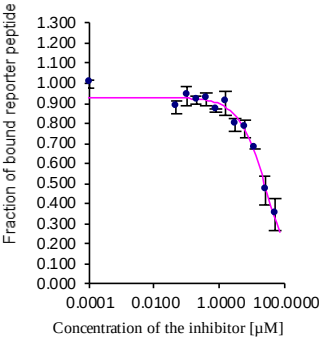
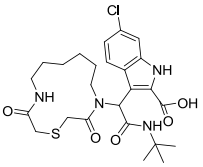
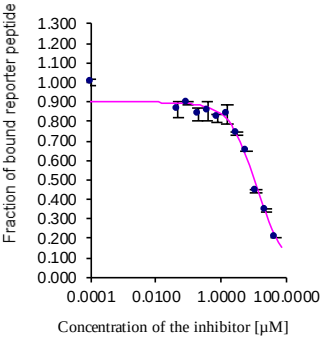
Table 6. Results of the evaluation of inhibitory activity of **6ad** compound towards MDM2/ MDMX.

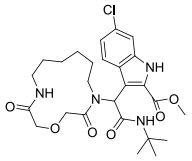
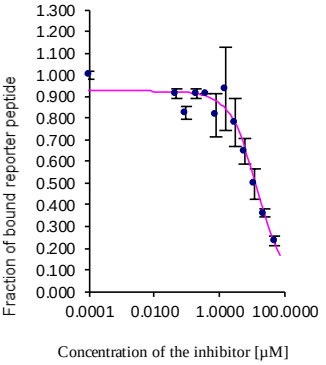
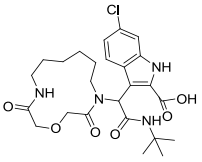
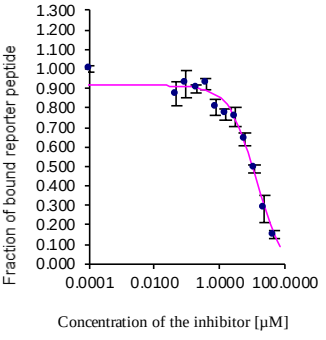
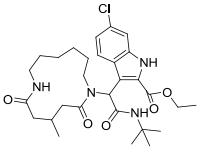
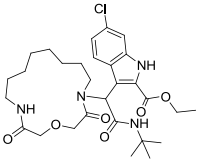
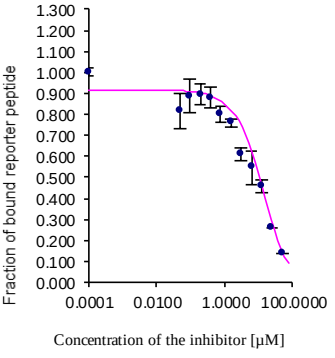
Comp.	Structure	K_i MDM2 [µM]	K_i MDMX [µM]	Plot
6ad		2.25	not active	

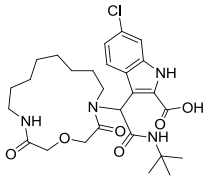
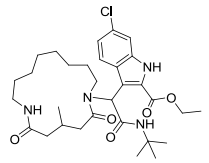
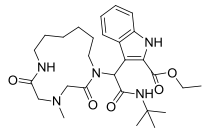
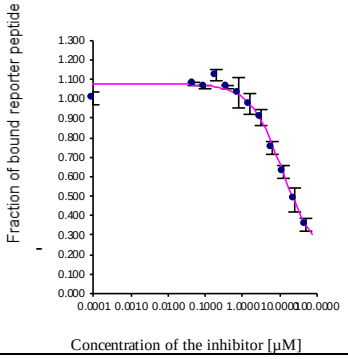
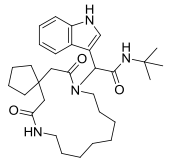
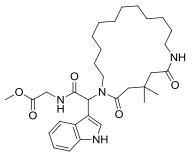
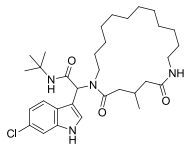
Furthermore, due to the importance of P53-MDM2/MDMX protein-protein interaction, there is more investigations are going to optimize the chemical synthesis strategy to obtained compounds with good solubility, more diversity and higher affinity to the receptor. Our group is currently working on the development of the macrocycles (data not published) using an amino acid linker with different sizes followed by cyclization-Ugi reaction with oxo compounds (anchor indole) and isocyanides (**Table 7**).

Table 7. Results of the evaluation of inhibitory activity of different derivatives of macrocycles towards MDM2/MDMX.

Entry	Structure	K_i MDM2 [µM]	K_i MDMX [µM]	Plot Concentration of inhibitor [µM] vs Fraction of bound receptor peptide
1		not active	not active	-

2		not active	not active	-
3		not active	not active	-
4		2.89	not active	
5		1.32	not active	

6		1.58	not active	
7		1.28	not active	
8		not active	not active	-
9		0.88	not active	

10		not active	not active	-
12		not active	not active	-
13		3.84	not active	- 
14		not active	not active	-
15		not active	not active	-
16		not active	not active	-

In summary, we have developed a general method that can quickly and accurately convert simple, broadly available, small molecule building blocks into macrocycles via a one pot Ugi-reaction. This robust and operationally simple 2-step, air- and moisture-tolerant procedure is a valuable addition to MCR chemistry and expands its unique scaffold diversity by giving access to 8−19 membered rings. Recent research suggests that passive cell permeability in cyclic peptides and non peptidic macrocycles sharply decreases at a MW of approximately 1000 Da.[24] However, the macrocyclic space of compounds less than 1000 Da remains largely unexplored and represents an interesting opportunity to chart new territories of drug discovery. The herein described unprecedented short 2-step synthesis of artificial macrocycles with 4 points of diversity covers this interesting chemical space and provides a fast entry to test binding hypothesis towards difficult intracellular targets.

Evaluation of inhibitory activity of macrocycles towards MDM2/MMDX:

Determination of dissociation constant of labeled peptide P2 and MDM2/MMDX

New protein stock (constructs: MDM2 1-118; MDMX 1-134) was thawed and the concentration was measured using Bradford method. Dissociation constant (K_d) of labeled peptide P2-Mdm2/MdmX was determined for further evaluation of optimal protein concentration for inhibition constant determination. Peptide P2 was labeled with carboxyfluorescein and had the following sequence: LTFEHYWAQLTS. K_d was determined for each thawed new protein stock using fluorescence polarization (FP) assay.

FP assay was performed in duplicates on 96-well microplates (Corning NBS 3991) in final volume 100 µl (70 µl protein + 5 µl DMSO + 25 µl P2). Protein dilutions were made in FP buffer (10 mM Tris-HCL pH 8.0, 1 mM EDTA, 50 mM NaCl) to have to concentrations appropriate for K_d determination: 1,07 µM for Mdm2 and 5,36 µM for MdmX. First column of the Corning NBS 3991 microplate was filled with protein, rest of the columns were filled with FP buffer. Next, serial dilutions of the protein (range from 750 to 0,012 nM final concentration on the plate for Mdm2 and from 3750 to 0,10 nM for MdmX) were prepared in columns 2-11, last column (12) contained only FP buffer. The highest protein concentration in first column (0,75 µM for Mdm2 and 3,75 µM for MdmX) corresponded to FP values of the peptide saturated with protein; whereas the FP buffer with no protein corresponded to FP values of the peptide alone. To all columns DMSO (Bioshop DMS555.500) previously distributed on Greiner PP 651201 microwell plate was added to protein dilutions on Corning NBS 3991 plate. After mixing and 15 min incubation at room temperature, 40 nM P2 peptide solution prepared in 15 ml Sarstedt Falcon and was added to every column (1-12) so that the final concentration of P2 peptide was 10 nM. FP measurements were made using BioTek Synergy H1 microplate reader. K_d was determined by fitting curve of *Equation 1*. to the experimental data.

Equation 1.

$$y = y_0 \frac{ax}{K_d + x}$$

where y_0: FP_{min}

a: $FP_{max} - FP_{min}$

x: protein concentration
y: FP value measured at the desired concentration.

Preparation of stock solutions:

macrocycles were dissolved in deuterated DMSO (Sigma Aldrich 175943-10G 08828EJ) to obtain 50 mM concentration. Provided compounds were fully dissolved at room temperature at 50 mM and gave yellowish solutions.

Determination of the inhibition constants of macrocycle compounds:

Optimal protein concentration for the measurement (f_0=0.8) was calculated based on the determined K_d value (**Table 6** and **Table 7**). FP assay was made using 96-well microplates (Corning NBS 3991) and final volumes of 100 µl (70 µl protein + 5 µl inhibitor + 25 µl P2).

Serial dilutions in DMSO (Bioshop DMS555.500) of the tested compound was prepared in duplicates on 96-well Greiner 651201 microplates (wells A2-H12). The dilutions ranged from 50 µM to 0.05 µM (final concentrations on the plate). Wells A1-F1 were filled with DMSO to obtain the P_{max}, P_{min} and P_{f0} values. Wells G1-H1 were controls filled with Nutlin 3 (Cayman Chemicals; control; final concentration 25 µM). Protein at the optimal concentration was prepared in 15 ml Sarstedt Falcon and added into A2-H12 and E1-H1 wells on Corning NBS 3991 96-well microplates. Wells A1-B1 contained protein at final concentrations of 0.75 µM for Mdm2 and 3.75 µM for MdmX in order to determine P_{max}, whereas wells C1-D1- FP buffer only (to determine P_{min}). Next, 5 µl of each inhibitor dilution was transferred from Greiner 651201 to Corning NBS plate, mixed and incubated for 15 minutes at room temperature. After incubation, 40 nM P2 peptide solution was added (to final 10 nM concentration of the P2) and FP measurements were made using BioTek Synergy H1 microplate reader. Inhibition constants (K_i) were determined by fitting curves into experimental values.

NMR measurement:

Uniform ^{15}N isotope labeling was achieved by expression of the protein in the M9 minimal media containing $^{15}NH_4Cl$ as the sole nitrogen source. The final step of purification of Mdm2 (residues 1−118, chosen to enable interactions of N-terminal Mdm2 part) for NMR consisted of gel filtration into the NMR buffer (50 mM phosphate buffer at pH 7.4 containing 150 mM NaCl, 5 mM DTT). Then, 10% (v/v) D_2O was added to the samples to provide a lock signal. All the spectra were recorded at 300 K using a Bruker Avance III 600 MHz spectrometer.

Computational modelling of compound 6ad:

Computational modelling of compound **6ad** was performed using MOLOC software.[25] The crystal structure of the interaction of p53 peptide bound to MDM2 receptor (PDB ID 1YCR) was used for modelling.[26] The 2D structure of compound **6ad** was converted into a 3D structure and energy minimized in the absence of the receptor. Next the 3D structure of compound **6ad** was manually placed into the MDM2 receptor and the indol ring of compound **6ad** was aligned to the indol ring of W23 of the p53 peptide. The tert-butyl amide group of compound **6ad** was oriented into the F19 pocket of MDM2 as seen in other small molecule MDM2 cocrystal structures (PDB ID 3TU1, 3TJ2, 4MDN).[27] Next the macrocycle was energy optimized in the MDM2 receptor using the standard settings of the

force filed of MOLOC. The structure was rendered using PYMOL (the PYMOL molecular graphics system, version 1.2r3pre, Schrödinger, LLC).

General Experimental Procedures:

Procedure A: General procedure for synthesis of α,ω–amino carboxylic acids:

Diamine **1** (1.0 mmol) was dissolved in THF (6 mL), then a solution of anhydride **2** (1.0 mmol) in THF (4 mL) was added dropwise during 30 mins. The reaction mixture was further stirred for 1h. Solvents were removed under vacuum. The crude mixture was purified by flash column chromatography using CH_2Cl_2:MeOH (1:9) to afford the product **3**.

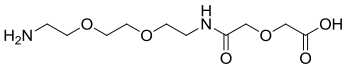
Procedure B: General procedure for Ugi-macrocyclization:

In an oven-dried 100 mL round bottom flask equipped with a magnetic stir bar, the α,ω–amino carboxylic acid 3 (1.0 mmol, 1 equiv.) was disolved in methanol (10.0 mL). Aldehyde 4 (1.0 mmol, 1.0 equiv.) was added and the solution was stirred for 30 min at rt, then isocyanide 5 (1.0 mmol, 1 equiv.) was added to the reaction mixture and the reaction mixture was diluted with methanol to 0.01M (+90 mL) and further stirred for 48 h. After completion of the reaction, as monitored by LC – MS, the reaction mixture was dried under reduced pressure via rotary evaporation and the residue was purified using flash chromatography (CH_2Cl_2: MeOH 9:1) to afford the product 6.

Procedure C: General procedure for one-pot macrocyclization:

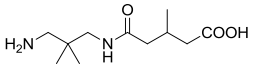
To the stirred solution of diamine **1** (1.0 mmol, 1.0 equiv.) in THF (6 mL) was added solution of anhydride **2** (1.0 mmol in 4mL THF) dropwise at 25 ^oC for 30 mins with dropping funnel. As soon as finished the addition of anhydride the reaction mixture was stirred for another 30 mins. Then after THF was removed under vacuum and refilled with methanol (0.01M) followed by addition of aldehyde/ketone and isocyanide at 25 ^oC stirred for 48 h. The reaction mixture was evaporated on rotavapor. The crude mixture obtained was purified by flash column chromatography using CH_2Cl_2: MeOH 9:1 to afford the macrocycle **6**.

14-Amino-5-oxo-3,9,12-trioxa-6-azatetradecan-1-oic acid 3a:



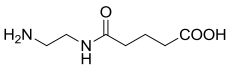
The product was obtained as a colorless oil (77%, 0.134g); ^1H NMR (500 MHz, D_2O) δ 4.00 (s, 2H), 3.94 (s, 2H), 3.66 (t, J = 5.1 Hz, 2H), 3.61 (s, 4H), 3.58 (t, J = 4.8 Hz, 2H), 3.38 (t, J = 5.2 Hz, 2H), 3.12 (t, J = 5.3 Hz, 2H); ^{13}C NMR (126 MHz, D_2O) δ 177.0, 172.6, 70.1, 69.5, 69.5, 69.4, 68.7, 66.4, 39.1, 38.4.

5-((3-Amino-2,2-dimethylpropyl)amino)-3-methyl-5-oxopentanoic acid 3b:



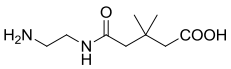
The product was obtained as a white solid (67%, 0.158g); ^1H NMR (500 MHz, Methanol-d_4) δ 3.04-2.91 (m, 2H), 2.61-2.52 (m, 2H), 2.30-2.15 (m, 2H), 2.12-2.02 (m, 1H), 2.02-1.91 (m, 2H), 0.90 (s, 9H); ^{13}C NMR (126 MHz, Methanol-d_4) δ 178.0, 174.1, 44.4, 44.0, 43.3, 41.1, 33.1, 27.5, 21.0, 17.8.

5-((2-Aminoethyl)amino)-5-oxopentanoic acid 3c:



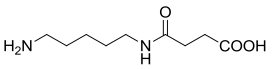
The product was obtained as a white solid (77%, 0.134g); ^{1}H NMR (500 MHz, D_2O) δ 3.49 (t, *J* = 5.9 Hz, 2H), 3.13 (t, *J* = 6.2 Hz, 2H), 2.28 (t, *J* = 7.5 Hz, 3H), 2.22 (t, *J* = 7.3 Hz, 3H), 1.83 (p, *J* = 7.2 Hz, 2H). ^{13}C NMR (126 MHz, D_2O) δ 181.7, 177.3, 39.1, 36.7, 35.9, 35.1, 21.6.

5-((2-Aminoethyl)amino)-3,3-dimethyl-5-oxopentanoic acid 3d:



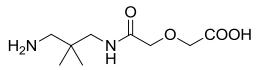
The product was obtained as a white solid (68%, 0.137g); ^{1}H NMR (500 MHz, D_2O) δ 3.50 (t, *J* = 6.1 Hz, 2H), 3.15 (t, *J* = 6.1 Hz, 2H), 2.29 (s, 2H), 2.17 (s, 2H), 1.05 (s, 6H). ^{13}C NMR (126 MHz, D_2O) δ 181.0, 176.0, 49.7, 47.5, 39.1, 36.6, 32.7, 27.5.

4-((5-Aminopentyl)amino)-4-oxobutanoic acid 3f:



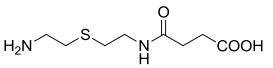
The product was obtained as a white solid (70%, 0.141g). ^{1}H NMR (500 MHz, D_2O) δ 3.08 (t, *J* = 6.7 Hz, 2H), 2.88 (t, *J* = 7.5 Hz, 2H), 2.36-2.33 (m, 4H), 1.62-1.50 (m, 2H), 1.49-1.37 (m, 2H), 1.31-1.22 (m, 2H); ^{13}C NMR (126 MHz, D_2O) δ 180.5, 175.6, 39.3, 38.8, 32.7, 32.2, 27.7, 26.3, 22.8.

2-(2-((3-Amino-2,2-dimethylpropyl)amino)-2-oxoethoxy)acetic acid 3g:



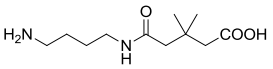
The product was obtained as a white solid (71%, 0.154g); ^{1}H NMR (500 MHz, D_2O) δ 4.02 (s, 2H), 3.91 (s, 2H), 3.09 (s, 2H), 2.70 (s, 2H), 0.92 (s, 6H); ^{13}C NMR (126 MHz, D_2O) δ 177.3, 173.5, 70.4, 69.4, 46.3, 45.5, 34.4, 22.3.

4-((2-((2-Aminoethyl)thio)ethyl)amino)-4-oxobutanoic acid 3h:



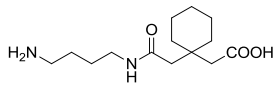
The product was obtained as a white solid (51%, 0.112g); ^{1}H NMR (500 MHz, D_2O) δ 3.28 (t, *J* = 6.6 Hz, 2H), 3.08 (t, *J* = 6.7 Hz, 2H), 2.74 (t, *J* = 6.7 Hz, 2H), 2.59 (t, *J* = 6.6 Hz, 2H), 2.34 (s, 4H); ^{13}C NMR (126 MHz, D_2O) δ 180.8, 176.0, 38.5, 38.3, 32.8, 32.2, 30.2, 28.1.

5-((4-Aminobutyl)amino)-3,3-dimethyl-5-oxopentanoic acid 3i:



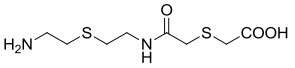
The product was obtained as a white solid (62%, 0.142g); ^{1}H NMR (500 MHz, D_2O) δ 3.12 (t, *J* = 6.7 Hz, 2H), 2.89 (t, *J* = 7.4 Hz, 2H), 2.14 (s, 2H), 2.07 (s, 2H), 1.64-1.53 (m, 2H), 1.53-1.46 (m, 2H), 0.95 (s, 6H); ^{13}C NMR (126 MHz, D_2O) δ 180.8, 174.8, 49.6, 47.7, 39.0, 38.4, 32.7, 27.4, 27.4, 25.5, 24.3.

2-(1-(2-((4-Aminobutyl)amino)-2-oxoethyl)cyclohexyl)acetic acid 3j:



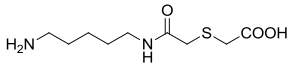
The product was obtained as a white solid (64%, 0.172g); ^{1}H NMR (500 MHz, D_2O) δ 3.12 (t, *J* = 6.7 Hz, 2H), 2.88 (t, *J* = 7.3 Hz, 2H), 2.24 (s, 2H), 2.16 (s, 2H), 1.65-1.54 (m, 2H), 1.53-1.43 (m, 2H), 1.41-1.34 (m, 4H), 1.34-1.23 (m, 6H); ^{13}C NMR (126 MHz, D_2O) δ 181.3, 175.0, 45.9, 44.2, 39.0, 38.3, 35.9, 35.9, 25.5, 24.3, 21.3.

2-((2-((2-((2-Aminoethyl)thio)ethyl)amino)-2-oxoethyl)thio)acetic acid 3l:



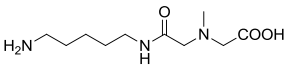
The product was obtained as a white solid (59%, 0.148g); ^{1}H NMR (500 MHz, D_2O) δ 3.36 (t, *J* = 6.5 Hz, 2H), 3.22 (s, 2H), 3.21 (s, 2H), 3.14 (t, *J* = 6.6 Hz, 2H), 2.79 (t, *J* = 6.6 Hz, 2H), 2.67 (t, *J* = 6.5 Hz, 2H); ^{13}C NMR (126 MHz, D_2O) δ 176.7, 172.4, 38.6, 38.3, 36.9, 35.5, 30.2, 28.2.

2-((2-((5-Aminopentyl)amino)-2-oxoethyl)thio)acetic acid 3m:



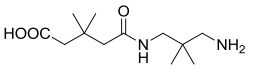
The product was obtained as a white solid (68%, 0.159g); ^{1}H NMR (500 MHz, D_2O) δ 3.18 (s, 2H), 3.15 (s, 2H), 3.13 (t, *J* = 6.8 Hz, 2H), 2.89 (t, *J* = 7.5 Hz, 2H), 1.62-1.52 (m, 2H), 1.51- 1.42 (m, 2H), 1.33-1.24 (m, 2H); ^{13}C NMR (126 MHz, D_2O) δ 176.7, 172.0, 39.3 (2xC), 36.9, 36.0, 27.7, 26.3, 22.9.

2-((2-((5-Aminopentyl)amino)-2-oxoethyl)(methyl)amino)acetic acid 3n:



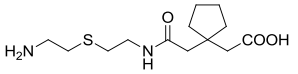
The product was obtained as a yellow oil (60%, 0.138g); ^{1}H NMR (500 MHz, D_2O) δ 3.13 (t, *J* = 6.7 Hz, 2H), 3.03 (s, 2H), 2.97 (s, 2H), 2.91-2.81 (m, 2H), 2.18 (s, 3H), 1.61-1.50 (m, 2H), 1.50-1.41 (m, 2H), 1.33-1.20 (m, 2H); ^{13}C NMR (126 MHz, D_2O) δ 178.7, 173.5, 61.3, 60.3, 42.5, 39.3, 38.6, 27.7, 26.3, 22.9.

5-((3-Amino-2,2-dimethylpropyl)amino)-3,3-dimethyl-5-oxopentanoic acid 3o:



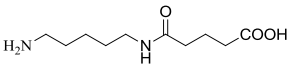
The product was obtained as a white solid (62%, 0.151g); ^{1}H NMR (500 MHz, D_2O) δ 3.03 (s, 2H), 2.69 (s, 2H), 2.20 (s, 2H), 2.10 (s, 2H), 0.96 (s, 6H), 0.91 (s, 6H). ^{13}C NMR (126 MHz, D_2O) δ 180.7, 175.8, 49.6, 47.6, 46.4, 46.0, 34.2, 32.7, 27.5, 22.4.

2-(1-(2-((2-((2-Aminoethyl)thio)ethyl)amino)-2-oxoethyl)cyclopentyl)acetic acid 3p:



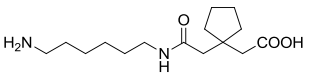
The product was obtained as a brown oil (72%, 0.207g); ^{1}H NMR (500 MHz, D_2O) δ 3.33 (t, *J* = 6.5 Hz, 2H), 3.12 (t, *J* = 6.7 Hz, 2H), 2.77 (t, *J* = 6.7 Hz, 2H), 2.65 (t, *J* = 6.5 Hz, 2H), 2.28 (s, 2H), 2.22 (s, 2H), 1.58-1.52 (m, 4H), 1.48-1.42 (m, 4H); ^{13}C NMR (126 MHz, D_2O) δ 181.1, 175.4, 45.8, 44.3, 44.0, 38.4, 38.2, 37.4 (2xC), 30.3, 28.1, 23.3 (2xC).

5-((5-Aminopentyl)amino)-5-oxopentanoic acid 3q:



The product was obtained as a yellow solid (81%, 0.174g); ^{1}H NMR (500 MHz, D_2O) δ 3.18 (t, *J* = 6.8 Hz, 2H), 2.98 (t, *J* = 7.3 Hz, 2H), 2.27-2.18 (m, 4H), 1.85-1.77 (m, 2H), 1.70-1.61 (m, 2H), 1.58-1.49 (m, 2H), 1.43 – 1.33 (m, 2H); ^{13}C NMR (126 MHz, D_2O) δ 181.6, 176.2, 39.3, 38.8, 35.9, 35.3, 27.7, 26.3, 22.9, 22.1.

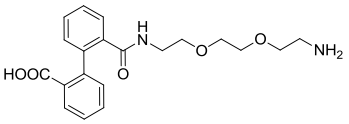
2-(1-(2-((6-aminohexyl)amino)-2-oxoethyl)cyclopentyl)acetic acid 3s:



The product was obtained as a white solid (72%, 0.204g); ^{1}H NMR (500 MHz, MeOD-d_4) δ 3.10-3.02 (m, 2H), 2.81-2.72 (m, 2H), 2.23 (s, 2H), 2.12 (s, 2H), 1.63-1.49 (m, 6H), 1.49-

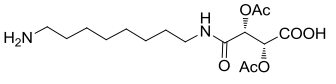
1.36 (m, 6H), 1.36-1.23 (m, 4H); ^{13}C NMR (126 MHz, MeOD-d_4) δ 177.1, 171.3, 43.8, 42.1, 42.0, 36.7, 35.7, 26.3, 26.2, 24.6, 23.6, 23.0, 21.2.

2'-((2-(2-(2-Aminoethoxy)ethoxy)ethyl)carbamoyl)-[1,1'-biphenyl]-2-carboxylic acid 3t:



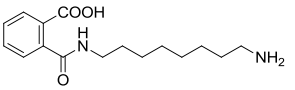
The product was obtained as a colorless oil (55%, 0.204g); ^{1}H NMR (500 MHz, D_2O) δ 7.55-7.51 (m, 1H), 7.46 (dd, *J* = 7.2, 1.8 Hz, 1H), 7.41-7.37 (m, 2H), 7.37-7.33 (m, 1H), 7.32-7.28 (m, 1H), 7.13-7.09 (m, 1H), 7.01-6.96 (m, 1H), 3.60 (t, *J* = 5.1 Hz, 2H), 3.49 (t, *J* = 4.4 Hz, 2H), 3.36-3.27 (m, 2H), 3.24-3.14 (m, 2H), 3.11-3.00 (m, 3H), 2.97-2.78 (m, 1H).; ^{13}C NMR (126 MHz, D_2O) δ 176.7, 172.3, 139.7, 138.3, 134.4, 130.3, 129.3, 129.1, 127.8, 127.7, 127.4, 127.2, 69.4, 69.4, 68.6, 66.3, 39.0, 39.0.

(2*R*,3*R*)-2,3-Diacetoxy-4-((8-aminooctyl)amino)-4-oxobutanoic acid 3w:



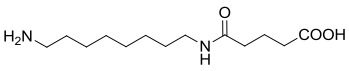
The product was obtained as a white solid (82%, 0.295g); ^{1}H NMR (500 MHz, D_2O) δ 5.43 (d, *J* = 2.5 Hz, 1H), 5.24 (d, *J* = 2.4 Hz, 1H), 3.19-3.04 (m, 2H), 2.89 (t, *J* = 7.6 Hz, 2H), 2.10 (s, 3H), 2.07 (s, 3H), 1.62-1.48 (m, 2H), 1.47-1.34 (m, 2H), 1.32-1.10 (m, 8H); ^{13}C NMR (126 MHz, D_2O) δ 172.7, 172.4, 171.9, 168.6, 73.4, 73.4, 39.5, 39.1, 28.2, 28.0, 27.9, 26.6, 25.6, 25.4, 20.1, 20.0.

2-((8-Aminooctyl)carbamoyl)benzoic acid 3x:



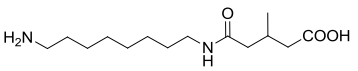
The product was obtained as a white solid (83%, 0.239g); ^{1}H NMR (500 MHz, MeOD-d_4) δ 7.47 (d, *J* = 7.5 Hz, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.31 (t, *J* = 7.3 Hz, 1H), 7.26 (t, *J* = 7.4 Hz, 1H), 3.23 (t, *J* = 6.9 Hz, 2H), 2.78 (t, *J* = 7.4 Hz, 2H), 1.56-1.46 (m, 4H), 1.33-1.25 (m, 8H); ^{13}C NMR (126 MHz, MeOD-d_4) δ 173.6, 169.2, 137.6, 132.5, 127.9, 126.4, 126.2, 126.1, 37.8, 37.7, 27.1, 26.6, 26.6, 25.3, 24.4, 23.9.

5-((8-Aminooctyl)amino)-5-oxopentanoic acid 3z:



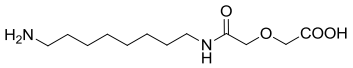
The product was obtained as a white solid (76%, 0.193g); ^{1}H NMR (500 MHz, D_2O) δ 3.06 (t, *J* = 6.7 Hz, 2H), 2.86 (t, *J* = 7.6 Hz, 2H), 2.12 (t, *J* = 7.5 Hz, 2H), 2.07 (t, *J* = 7.6 Hz, 2H), 1.77 – 1.66 (m, 2H), 1.61 – 1.48 (m, 2H), 1.46 – 1.34 (m, 2H), 1.29 – 1.15 (m, 8H); ^{13}C NMR (126 MHz, D_2O) δ 182.4, 176.1, 39.4, 39.2, 36.7, 35.5, 28.1, 28.0, 27.9, 26.6, 25.7, 25.4, 22.6.

5-((8-aminooctyl)amino)-3-methyl-5-oxopentanoic acid 3ab:



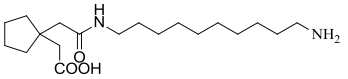
The product was obtained as a white solid (75%, 0.204g); ^{1}H NMR (500 MHz, Methanol-d_4) δ 2.98 – 2.84 (m, 2H), 2.67 – 2.59 (m, 2H), 2.10 – 1.96 (m, 2H), 1.91 (dd, *J* = 13.9, 6.3 Hz, 1H), 1.83 – 1.69 (m, 2H), 1.46 – 1.33 (m, 2H), 1.31 – 1.19 (m, 2H), 1.18 – 1.03 (m, 8H), 0.71 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, Methanol-d_4) δ 178.1, 172.1, 43.2, 41.5, 37.6, 37.1, 27.5, 27.3, 27.0, 26.9, 25.5, 24.7, 24.2, 17.3.

2-(2-((8-aminooctyl)amino)-2-oxoethoxy)acetic acid 3ad:



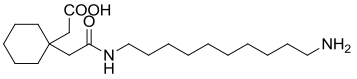
The product was obtained as a colorless oil (74%, 0.192g); ^{1}H NMR (500 MHz, Methanol-d_4) δ 3.92 (s, 2H), 3.89 (s, 2H), 3.16 (t, *J* = 7.0 Hz, 2H), 2.84 (d, *J* = 8.3 Hz, 2H), 1.58 (p, *J* = 7.3 Hz, 2H), 1.52-1.43 (m, 2H), 1.34-1.25 (m, 8H); ^{13}C NMR (126 MHz, Methanol-d_4) δ 173.8, 169.3, 68.7, 68.3, 37.6, 36.9, 27.3, 27.0, 27.0, 25.5, 24.8, 24.3.

2-(1-(2-((10-aminodecyl)amino)-2-oxoethyl)cyclopentyl)acetic acid 3ag:



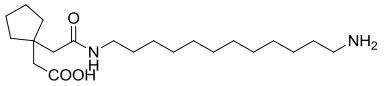
The product was obtained as a white solid (75%, 0.255g); ^{1}H NMR (500 MHz, D_2O) δ 3.24 (t, *J* = 6.6 Hz, 2H), 3.03 (t, *J* = 8.4 Hz, 2H), 2.40 (s, 2H), 2.32 (s, 2H), 1.75-1.65 (m, 6H), 1.65-1.52 (m, 6H), 1.45-1.31 (m, 12H); ^{13}C NMR (126 MHz, D_2O) δ 181.4, 175.0, 46.4, 44.4, 44.0, 39.5, 39.1, 37.2, 28.3, 28.2, 28.1, 28.0, 26.6, 26.0, 25.4, 23.4.

2-(1-(2-((10-aminodecyl)amino)-2-oxoethyl)cyclohexyl)acetic acid 3ah:



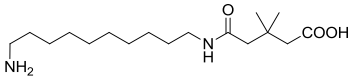
The product was obtained as a white solid (80%, 0.327g); ^{1}H NMR (500 MHz, Methanol-d4) δ 3.21 (t, J = 6.9, 4.0 Hz, 2H), 2.99-2.88 (m, 2H), 2.41 (s, 2H), 2.33 (s, 2H), 1.78 -1.63 (m, 2H), 1.62-1.50 (m, 6H), 1.50 – 1.31 (m, 18H). ^{13}C NMR (126 MHz, Methanol-d4) δ 178.7, 173.2, 45.6, 43.8, 39.3, 38.8, 36.6, 35.7, 29.1, 28.9, 28.8, 28.7, 28.6, 27.1, 26.6, 26.0, 25.8, 21.4.

2-(1-(2-((12-Aminododecyl)amino)-2-oxoethyl)cyclopentyl)acetic acid 3ai:



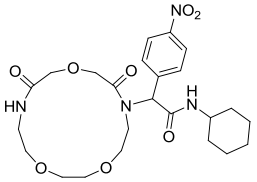
The product was obtained as a white solid (74%, 0.272g); ^{1}H NMR (500 MHz, MeOD-d_4) δ 3.19 (t, *J* = 6.1 Hz, 2H), 2.91 (t, *J* = 7.7 Hz, 2H), 2.36 (s, 2H), 2.26 (s, 2H), 1.76-1.62 (m, 6H), 1.61- 1.55 (m, 4H), 1.54-1.47 (m, 2H), 1.43-1.29 (m, 16H); ^{13}C NMR (126 MHz, MeOD-d_4) δ 177.8, 172.0, 44.6, 42.8, 42.7, 37.8, 37.2, 36.3, 27.5, 27.3, 27.3, 27.2, 27.0, 25.6, 25.0, 24.4, 22.0.

5-((10-Aminodecyl)amino)-3,3-dimethyl-5-oxopentanoic acid 3aj:



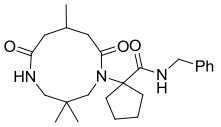
The product was obtained as a white solid (80%, 0.251g); 1H NMR (500 MHz, D_2O) δ 3.17 (t, *J* = 6.7 Hz, 2H), 2.97 (t, *J* = 7.4 Hz, 2H), 2.24 (s, 2H), 2.18 (s, 2H), 1.72-1.60 (m, 2H), 1.55-1.43 (m, 2H), 1.36-1.25 (m, 12H), 1.05 (s, 6H); ^{13}C NMR (126 MHz, D_2O) δ 180.8, 174.5, 49.8, 48.8, 47.7, 39.5, 39.2, 32.8, 28.4, 28.3, 28.3, 28.2, 28.1, 27.5, 26.7, 26.1, 25.5.

N-cyclohexyl-2-(8,12-dioxo-1,4,10-trioxa-7,13-diazacyclopentadecan-7-yl)-2-(4-nitrophenyl)acetamide 6a:



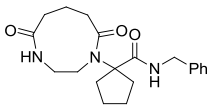
Prepared according to procedure **B** and purified by column chromatography using CH_2Cl_2:MeOH isolated as a white solid (55%, 0.278g). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.27-8.13 (m, 3H), 7.72 (t, *J* = 5.6 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 2H), 6.01 (s, 1H), 4.66-4.50 (m, 2H), 3.99 (s, 2H), 3.66-3.56 (m, 1H), 3.56-3.41 (m, 6H), 3.34-3.27 (m, 4H), 3.27-3.20 (m, 1H), 3.15-3.04 (m, 1H), 1.84-1.73 (m, 2H), 1.73-1.62 (m, 2H), 1.59-1.50 (m, 1H), 1.34-1.22 (m, 2H), 1.22-1.07 (m, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.7, 169.6, 167.4, 147.3, 145.4, 130.1, 123.8, 69.8, 69.6, 69.5, 69.5, 68.3, 67.8, 61.0, 48.4, 45.6, 38.3, 32.6, 25.6, 25.0. HRMS (ESI) m/z calculated for $C_{24}H_{35}N_4O_8$ $[M+H]^+$: 507.2449; found $[M+H]^+$: 507.2447.

N-Benzyl-1-(3,3,8-trimethyl-6,10-dioxo-1,5-diazecan-1-yl)cyclopentanecarboxamide 6b:



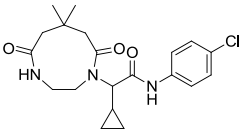
Prepared according to procedure **B** and purified by column chromatography using CH_2Cl_2:MeOH isolated as colorless oil (38%, 0.157g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (br s, 1H), 7.33-7.30 (m, 4H), 7.29-7.26 (m, 1H), 6.94 (t, *J* = 5.5 Hz, 1H), 4.71-4.55 (m, 2H), 4.39 (dd, *J* = 14.5, 5.4 Hz, 1H), 3.62 (dd, *J* = 12.3, 5.8 Hz, 1H), 2.64 (d, *J* = 13.0 Hz, 1H), 2.62-2.54 (m, 1H), 2.49 (d, *J* = 14.3 Hz, 1H), 2.34-2.28 (m, 1H), 2.05-1.94 (m, 5H), 1.93 – 1.86 (m, 3H), 1.82-1.75 (m, 1H), 1.69-1.57 (m, 2H), 1.28 (s, 3H), 0.87 (s, 3H), 0.75 (d, *J* = 6.9 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 177.6, 176.0, 174.3, 138.1, 128.8, 128.0, 127.6, 73.6, 52.3, 50.3, 44.3, 44.0, 43.9, 40.9, 38.5, 34.5, 33.1, 28.3, 25.8, 24.4, 23.3. HRMS (ESI) m/z calculated for $C_{24}H_{36}N_3O_3$ $[M+H]^+$: 414.2751; found $[M+H]^+$: 414.2746.

N-Benzyl-1-(5,9-dioxo-1,4-diazonan-1-yl)cyclopentanecarboxamide 6c:



Prepared according to procedure **B** and purified by column chromatography using CH_2Cl_2:MeOH isolated as semi-solid (27%, 0.096g); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39-7.33 (m, 4H), 7.32-7.29 (m, 1H), 7.27-7.22 (m, 1H), 6.48 (t, *J* = 5.7 Hz, 1H), 4.54-4.40 (m, 2H), 3.99-3.89 (m, 1H), 3.88-3.78 (m, 1H), 3.25 (dd, *J* = 15.8, 4.4 Hz, 1H), 2.97-2.87 (m, 1H), 2.69-2.59 (m, 1H), 2.45-2.38 (m, 1H), 2.32-2.18 (m, 3H), 2.11-2.05 (m, 2H), 2.03-1.96 (m, 1H), 1.96-1.88 (m, 1H), 1.86-1.79 (m, 1H), 1.78-1.65 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.8, 175.8, 175.8, 138.2, 128.7, 127.6, 127.5, 73.3, 44.3, 43.9, 38.8, 36.8, 35.4, 33.7, 29.2, 23.8, 23.6, 22.9; HRMS (ESI) m/z calculated for $C_{20}H_{28}N_3O_3$ $[M+H]^+$: 358.2125; found $[M+H]^+$: 358,2125.

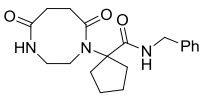
N-(4-Chlorophenyl)-2-cyclopropyl-2-(3,3-dimethyl-6,9-dioxo-1,5-diazonan-1-yl) acetamide 6d:



Prepared according to procedure **B** and purified by column chromatography using CH_2Cl_2:MeOH isolated as a white solid (59%, 0.230g). ^{1}H NMR (500 MHz, $CDCl_3$, rotamers were observed) δ 8.94 (s, 1H), 7.49 (d, *J* = 8.8 Hz, 2H), 7.27 (d, *J* = 8.8 Hz, 2H), 6.64 (dd, *J* = 10.9, 3.5 Hz, 1H), 3.72 (dd, *J* = 15.0, 11.4 Hz, 1H), 3.63 (d, *J* = 15.5 Hz, 1H), 2.83 (t, *J* = 12.0 Hz, 2H), 2.75-2.69 (m, 3H), 2.64-2.57

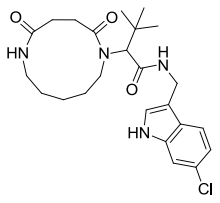
(m, 1H), 1.96-1.86 (m, 1H), 1.08 (s, 3H), 0.97-0.93 (m, 1H), 0.92 (s, 3H), 0.89-0.83 (m, 1H), 0.78-0.71 (m, 1H), 0.58-0.52 (m, 1H), 0.52-0.46 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$, rotamers were observed) δ 175.9, 174.0, 168.2, 136.4, 129.3, 128.9, 121.6, 72.2, 57.9, 48.9, 39.7, 31.3, 28.9, 24.8, 24.0, 10.7, 4.4, 3.9. HRMS (ESI) m/z calculated for $C_{20}H_{27}ClN_3O_3$ $[M+H]^+$: 392.1733; found $[M+H]^+$: 392.1734.

N-Benzyl-1-(5,8-dioxo-1,4-diazocan-1-yl)cyclopentanecarboxamide 6e:



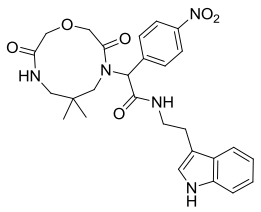
Prepared according to procedure **C** and purified by column chromatography using CH_2Cl_2:MeOH isolated as white solid (50%, 0.171g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 5.5 Hz, 1H), 7.35- 7.30 (m, 2H), 7.29 – 7.25 (m, 3H), 6.26 (t, *J* = 5.6 Hz, 1H), 4.41 (d, *J* = 5.8 Hz, 2H), 3.68 (t, *J* = 6.1 Hz, 2H), 3.35 (q, *J* = 6.0 Hz, 2H), 2.79 (t, *J* = 7.2 Hz, 2H), 2.69-2.63 (m, 2H), 2.59 (t, *J* = 7.2 Hz, 2H), 1.83-1.76 (m, 2H), 1.74-1.65 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.7, 174.6, 172.8, 138.4, 128.7, 127.7, 127.3, 73.3, 46.7, 43.7, 42.2, 36.0, 33.7, 31.2, 22.3. HRMS (ESI) m/z calculated for $C_{19}H_{26}N_3O_3$ $[M+H]^+$: 344.1968; found $[M+H]^+$: 344,1969.

N-((6-Chloro-1H-indol-3-yl)methyl)-2-(2,5-dioxo-1,6-diazacycloundecan-1-yl)-3,3-dimethylbutanamide 6f:



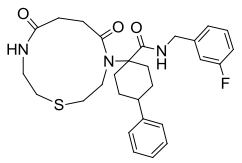
Prepared according to procedure **B** and purified by column chromatography using CH_2Cl_2:MeOH isolated as yellow semisolid (51%, 234g). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.10 (s, 1H), 8.08 (s, 1H), 7.89 (d, *J* = 9.4 Hz, 1H), 7.63 (d, *J* = 5.8 Hz, 1H), 7.46 (s, 1H), 7.40 (s, 1H), 7.02 (d, *J* = 7.2 Hz, 1H), 4.57 (dd, *J* = 14.5, 4.2 Hz, 1H), 4.30-4.17 (m, 2H), 4.18-4.04 (m, 1H), 3.68 (d, *J* = 11.5 Hz, 1H), 3.54- 3.39 (m, 2H), 3.23-3.14 (m, 2H), 2.57-2.53 (m, 1H), 2.25-2.12 (m, 1H), 2.02-1.91 (m, 1H), 1.68-1.57 (m, 1H), 1.35-1.11 (m, 4H), 0.94 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.5, 171.9, 168.9, 137.1, 126.3, 125.9, 125.8, 120.5, 119.3, 112.4, 111.4, 67.7, 44.9, 39.0, 37.9, 36.2, 34.3, 30.4, 28.4, 27.8, 27.3, 21.2. HRMS (ESI) m/z calculated for $C_{24}H_{34}ClN_4O_3$; found:461.2316; found $[M+H]^+$: 461.23157.

N-(2-(1H-Indol-3-yl)ethyl)-2-(6,6-dimethyl-3,9-dioxo-1,4,8-oxadiazecan-4-yl)-2-(4-nitrophenyl)acetamide 6g:



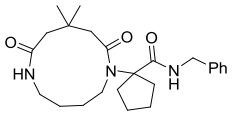
Prepared according to procedure **B** and purified by column chromatography using CH_2Cl_2:MeOH isolated as semi solid (50%, 0.260g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (s, 1H), 8.15 – 8.11 (m, 2H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.45-7.41 (m, 2H), 7.39 (d, *J* = 8.1 Hz, 1H), 7.24-7.20 (m, 2H), 7.17-7.12 (m, 2H), 7.01 (d, *J* = 2.1 Hz, 1H), 4.33 (s, 4H), 4.12 (s, 1H), 3.73-3.66 (m, 2H), 3.66-3.62 (m, 2H), 3.06-3.00 (m, 2H), 2.22 (d, *J* = 11.8 Hz, 1H), 2.11 (d, *J* = 11.9 Hz, 1H), 0.80 (s, 3H), 0.75 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 170.1, 147.5, 146.6, 136.4, 128.2, 127.4, 123.8, 122.2, 122.1, 119.5, 118.7, 112.6, 111.3, 67.8, 67.7, 57.0, 44.0, 39.3, 36.4, 25.0, 24.5, 24.2. HRMS (ESI) m/z calculated for $C_{27}H_{32}N_5O_6$ $[M+H]^+$: 522.23499; found $[M+H]^+$: 522.23486.

1-(5,8-Dioxo-1-thia-4,9-diazacycloundecan-4-yl)-N-(3-fluorobenzyl)-4-phenyl cyclohexanecarboxamide 6h:



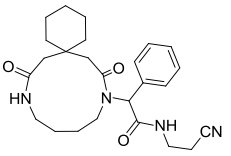
Prepared according to procedure **B** and purified by column chromatography using CH_2Cl_2:MeOH isolated as yellow semisolid (33%, 0.175g), ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (t, *J* = 5.5 Hz, 1H), 7.27 (t, *J* = 7.4 Hz, 3H), 7.17 (t, *J* = 7.3 Hz, 1H), 7.12 (d, *J* = 7.4 Hz, 2H), 7.08 (d, *J* = 7.7 Hz, 1H), 7.06-7.01 (m, 1H), 6.92 (t, *J* = 7.5 Hz, 1H), 6.03 (br s, 1H), 4.75-4.60 (m, 1H), 4.25-4.12 (m, 1H), 3.78 (br s, 1H), 3.56-3.48 (m, 2H), 3.24-3.13 (m, 1H), 3.12-3.00 (m, 1H), 2.87-2.70 (m, 4H), 2.65-2.57 (m, 2H), 2.56-2.49 (m, 1H), 2.47-2.40 (m, 1H), 2.24-2.09 (m, 2H), 2.01-1.85 (m, 2H), 1.84-1.67 (m, 2H), 1.45-1.34 (m, 1H), 1.27-1.15 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.8, 175.4, 173.0, 162.92 (d, *J* =245.7 Hz), 145.8, 141.5 (d, *J* = 7.0 Hz), 130.1 (d, *J* = 8.0 Hz), 128.5, 126.5, 126.4, 123.0, 114.3 (d, *J* = 22.1 Hz), 114.0 (d, *J* =21.1 Hz), 64.4, 46.0, 42.8, 39.8, 34.6, 34.2, 34.0, 32.8, 31.4, 30.5, 29.6, 29.0. HRMS (ESI) m/z calculated for $C_{28}H_{35}FN_3O_3S$ $[M+H]^+$:534.21973; found $[M+H]^+$: 534.21979.

N-Benzyl-1-(9,9-dimethyl-7,11-dioxo-1,6-diazacycloundecan-1-yl)cyclopentane-carboxamide 6i:



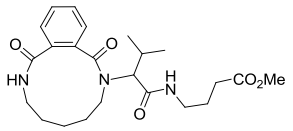
Prepared according to procedure **B** and purified by column chromatography using CH_2Cl_2:MeOH isolated as white solid (31% yield, 0.128g); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (t, *J* = 6.3 Hz, 1H), 7.43 (d, *J* = 7.2 Hz, 2H), 7.37 (t, *J* = 8.4, 6.7 Hz, 2H), 7.32-7.29 (m, 1H), 6.14 (t, *J* = 5.8 Hz, 1H), 4.74-4.57 (m, 1H), 4.50-4.35 (m, 1H), 3.96 (s, 1H), 3.68- 3.45 (m, 1H), 3.37-3.22 (m, 1H), 2.84-2.58 (m, 3H), 2.40-2.27 (m, 1H), 2.26-2.14 (m, 1H), 1.99-1.82 (m, 6H), 1.82-1.62 (m, 6H), 1.40 (s, 3H), 1.21 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.3, 173.6, 171.6, 138.3, 128.7, 127.7, 127.4, 73.2, 45.9, 44.8, 44.0, 42.1, 40.1, 36.0, 35.8, 34.8, 30.9, 30.0, 29.4, 27.6, 24.3, 23.6; HRMS (ESI) m/z calculated for $C_{24}H_{35}N_3NaO_3$ $[M+Na]^+$: 436.2571; found $[M+Na]^+$: 436.2570.

N-(2-Cyanoethyl)-2-(8,15-dioxo-9,14-diazaspiro[5.10]hexadecan-9-yl)-2-phenylacetamide 6j:



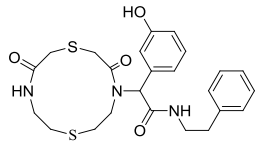
Prepared according to procedure **B** and purified by column chromatography using CH_2Cl_2:MeOH isolated as semi-solid (25%, 0.109g); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23-8.12 (m, 1H), 7.48-7.40 (m, 3H), 7.39-7.34 (m, 2H), 5.86 (t, *J* = 6.3 Hz, 1H), 4.56 (s, 1H), 4.01-3.91 (m, 1H), 3.70-3.60 (m, 1H), 3.57-3.42 (m, 2H), 3.06-2.95 (m, 1H), 2.81-2.67 (m, 2H), 2.63-2.53 (m, 1H), 2.49-2.41 (m, 1H), 2.34-2.27 (m, 1H), 2.24 (d, *J* = 12.4 Hz, 1H), 2.13 (d, *J* = 12.4 Hz, 1H), 2.00 (br s, 1H), 1.93-1.80 (m, 5H), 1.79-1.72 (m, 1H), 1.68-1.56 (m, 2H), 1.54-1.38 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4, 171.5, 171.4, 134.0, 129.6, 129.4, 129.2, 117.9, 66.4, 48.7, 43.3, 39.9, 38.1, 37.9, 37.2, 36.3, 27.4, 27.2, 26.2, 21.9, 21.8, 17.6; HRMS (ESI) m/z calculated for $C_{25}H_{35}N_4O_3$ $[M+H]^+$: 439.2704; found $[M+H]^+$: 439.2701.

Methyl 4-(2-(1,9-dioxo-4,5,6,7,8,9-hexahydro-1H-benzo[c][1,6]diazacycloundecin-2(3H)-yl)-3-methylbutanamido)butanoate 6k:



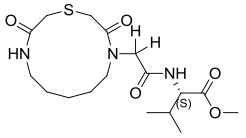
Prepared according to procedure **B** and purified by column chromatography using CH_2Cl_2:MeOH isolated as white solid (42%, 0.181g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 7.4, 1.5 Hz, 1H), 7.51-7.42 (m, 2H), 7.28 (dd, *J* = 7.4, 1.4 Hz, 1H), 6.53 (d, *J* = 7.2 Hz, 1H), 6.51-6.46 (m, 1H), 4.03 – 3.96 (m, 1H), 3.92-3.83 (m, 1H), 3.61 (s, 3H), 3.46-3.30 (m, 2H), 3.14 (d, *J* = 10.5, 1H), 3.09-2.97 (m, 1H), 2.90-2.79 (m, 1H), 2.39-2.34 (m, 1H), 2.32 (t, *J* = 7.6 Hz, 2H), 1.92-1.81 (m, 3H), 1.68-1.52 (m, 3H), 1.51- 1.39 (m, 1H), 1.21-1.13 (m, 1H), 0.82 (d, *J* = 6.9 Hz, 3H), 0.64 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.7, 172.8, 169.6, 168.6, 134.8, 134.2, 130.8, 129.7, 128.7, 128.2, 68.5, 51.8, 42.1, 40.3, 39.3, 31.7, 29.0, 28.5, 26.6, 24.5, 20.9, 19.6, 19.0. HRMS (ESI) m/z calculated for $C_{23}H_{34}N_3O_3$ $[M+H]^+$: 432.2493; found $[M+H]^+$: 432.2493.

2-(3,11-Dioxo-1,7-dithia-4,10-diazacyclododecan-4-yl)-2-(3-hydroxyphenyl)-N-phenethylacetamide 6l:



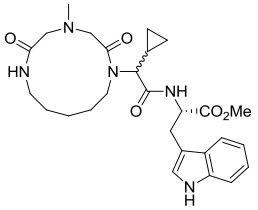
Prepared according to procedure **B** and purified by column chromatography using CH_2Cl_2:MeOH isolated as yellow solid (72%, 0.350g). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.54 (s, 1H), 8.55 (t, *J* = 5.7 Hz, 1H), 8.25 (t, *J* = 5.5 Hz, 1H), 7.31-7.23 (m, 2H), 7.22-7.17 (m, 3H), 7.15 (t, *J* = 7.9 Hz, 1H), 6.73 (dd, *J* = 8.1, 2.2 Hz, 1H), 6.66 (s, 1H), 6.58 (d, *J* = 7.7 Hz, 1H), 5.91 (s, 1H), 3.57-3.45 (m, 4H), 3.42-3.35 (m, 2H), 3.30-3.22 (m, 2H), 3.13 (s, 2H), 2.80-2.62 (m, 4H), 2.60-2.53 (m, 1H), 2.06-1.95 (m, 1H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.3, 169.0, 168.8, 157.9, 139.8, 137.8, 130.1, 129.1, 128.8, 126.6, 120.1, 116.4, 115.6, 60.4, 46.8, 43.2, 40.8, 35.6, 35.4, 33.4, 30.8, 30.0. HRMS (ESI) m/z calculated for $C_{24}H_{30}N_3O_4S_2$ $[M+H]^+$: 488.16653; found $[M+H]^+$: 488.16675.

Methyl 2-(2-(3,11-dioxo-1-thia-4,10-diazacyclododecan-4-yl)acetamido)-3-methyl butanoate 6m:



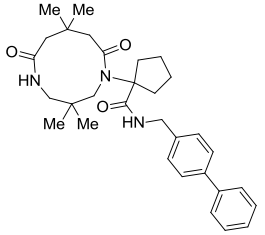
Prepared according to procedure **B** and purified by column chromatography using CH_2Cl_2:MeOH isolated as white solid (42%, 0.162g). ^{1}H NMR (500 MHz, Chloroform-d, rotamers were observed) δ 6.60 (t, *J* = 8.4 Hz, 1H), 4.61-4.55 (m, 1H), 4.55-4.44 (m, 1H), 4.38-4.18 (m, 1H), 4.04-3.85 (m, 1H), 3.74 (s, 3H), 3.70-3.59 (m, 1H), 3.55-3.39 (m, 2H), 3.35-3.27 (m, 2H), 2.91 (t, *J* = 12.4 Hz, 1H), 2.69-2.56 (m, 1H), 2.26-2.15 (m, 1H), 1.92-1.82 (m, 2H), 1.64-1.53 (m, 2H), 1.46-1.34 (m, 2H), 1.21-1.10 (m, 1H), 0.97-0.89 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$, rotamers were observed) δ 173.1, 172.5, 171.2, 168.2, 57.7, 52.1, 47.9, 40.6, 38.3, 37.3, 35.7, 30.7, 26.7, 24.6, 19.2, 17.9. HRMS (ESI) m/z calculated for $C_{17}H_{30}N_3O_5S$ $[M+H]^+$: 388.19034; found $[M+H]^+$: 388.19025.

Methyl 2-(2-cyclopropyl-2-(4-methyl-2,6-dioxo-1,4,7-triazacyclododecan-1-yl)acetamido)-3-(1H-indol-3-yl)propanoate 6n:



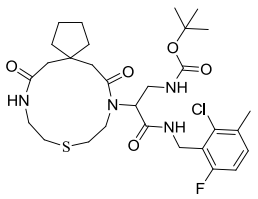
Prepared according to procedure **B** and purified by column chromatography using CH_2Cl_2:MeOH isolated as yellow semisolid (35%, 0.178g). ^{1}H NMR (500 MHz, $CDCl_3$, 1:1 diastereomeric ratio) δ 8.70 (s, 1H), 8.57 (s, 1H), 7.55 (d, *J* = 7.9 Hz, 2H), 7.52-7.46 (m, 1H), 7.40-7.29 (m, 3H), 7.22-7.13 (m, 3H), 7.14-7.05 (m, 5H), 4.96-4.87 (m, 2H), 3.74 (s, 3H), 3.69 (s, 3H), 3.49 (s, 1H), 3.47-3.31 (m, 7H), 3.27-3.18 (m, 2H), 3.17-3.06 (m, 2H), 3.08-2.93 (m, 7H), 2.43 (s, 3H), 2.39 (s, 3H), 2.26-2.07 (m, 3H), 1.83-1.61 (m, 3H), 1.62-1.34 (m, 11H), 0.69-0.49 (m, 4H), 0.32-0.13 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$, 1:1 diastereomeric ratio) δ 172.5, 172.6, 170.6, 170.6, 170.5, 170.3, 170.0, 169.8, 136.2, 136.2, 127.5, 127.5, 123.5, 123.1, 122.1, 122.0, 119.4, 119.4, 118.5, 111.4, 111.3, 109.7, 109.4, 64.0, 63.9, 63.1, 62.4, 58.9, 58.4, 52.7, 52.4, 52.3, 45.8, 45.6, 44.2, 44.1, 39.6, 39.6, 27.6, 27.5, 27.3, 26.2, 26.0, 24.6, 24.2, 9.8, 9.3, 5.9, 5.7, 3.5, 3.5. HRMS (ESI) m/z calculated for $C_{27}H_{38}N_5O_5$ $[M+H]^+$: 512.2867; found $[M+H]^+$: 512.2867.

N-([1,1'-Biphenyl]-4-ylmethyl)-1-(3,3,8,8-tetramethyl-6,10-dioxo-1,5-diazecan-1-yl)cyclopentanecarboxamide 6o:



Prepared according to procedure **B** and purified by column chromatography using CH_2Cl_2:MeOH isolated as white solid (37%, 0.186g). ^{1}H NMR (500 MHz, Methanol-d4) δ 7.64-7.55 (m, 4H), 7.53-7.47 (m, 2H), 7.44 (t, *J* = 8.0 Hz, 2H), 7.39-7.30 (m, 1H), 4.59 (dd, *J* = 14.5, 2.7 Hz, 1H), 4.54-4.40 (m, 2H), 3.50 (dd, *J* = 12.9, 2.7 Hz, 1H), 2.74-2.59 (m, 3H), 2.55-2.44 (m, 1H), 2.34 (dd, *J* = 12.1, 2.6 Hz, 1H), 2.22 (dd, *J* = 14.3, 2.7 Hz, 1H), 2.12-2.01 (m, 1H), 2.01-1.89 (m, 3H), 1.89-1.82 (m, 1H), 1.74-1.53 (m, 3H), 1.36 (s, 3H), 1.33 (s, 3H), 0.94 (s, 3H), 0.56 (s, 3H); ^{13}C NMR (126 MHz, Methanol-d4) δ 176.2, 175.2, 172.4, 139.1, 138.8, 136.3, 126.9, 126.9, 125.4, 125.3, 125.0, 72.7, 50.4, 48.3, 45.0, 44.5, 41.8, 38.8, 36.8, 35.8, 32.8, 32.1, 25.5, 25.4, 22.8, 22.3. HRMS (ESI) m/z calculated for $C_{31}H_{42}N_3O_3$ $[M+H]^+$: 504.3221; found $[M+H]^+$: 504.3221.

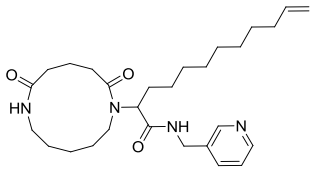
***tert*-Butyl (3-((2-chloro-4-fluoro-3-methylbenzyl)amino)-2-(7,15-dioxo-11-thia-8,14-diazaspiro[4.11]hexadecan-8-yl)-3-oxopropyl)carbamate 6p:**



Prepared according to procedure **B** and purified by column chromatography using CH_2Cl_2:MeOH isolated as yellow semisolid (26%, 0.159g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (br s, 1H), 7.18 (dd, *J* = 8.4, 6.1 Hz, 1H), 6.94 (t, *J* = 8.7 Hz, 1H), 5.95 (s, 1H), 5.20 (s, 1H), 4.79 (dd, *J* = 14.0, 5.9 Hz, 1H), 4.55(dd, *J* = 14.1, 3.3 Hz, 1H), 4.05 (s, 1H), 3.81-3.58 (m, 2H), 3.55-3.48 (m, 1H), 3.47-3.39 (m, 1H), 3.01 (s, 1H), 2.92-2.82 (m, 2H), 2.76-2.70 (m, 2H), 2.35 (s, 3H), 2.26 (d, *J* = 12.6, 1H), 2.19 (d, *J* = 12.6 Hz, 1H), 2.10-2.01 (m, 1H), 1.92-1.82 (m, 2H), 1.71-1.62 (m, 3H), 1.62-1.54 (m, 2H), 1.49-1.44 (m, 3H), 1.43 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.1, 172.4, 169.7, 159.7 (d, *J* =247.8 Hz), 156.1, 135.3 (d, *J* = 5.0Hz), 132.6 (d, *J* = 3.6Hz), 130.8 (d, *J* = 9.0 Hz), 123.4 (d, *J* = 17.7 Hz), 113.8 (d, *J* = 22.5 Hz), 79.9, 59.6, 46.5, 44.4, 43.6, 41.2, 39.5, 39.1, 38.7, 38.0,

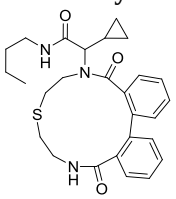
35.3, 35.3, 34.2, 32.7, 28.3, 23.9, 23.6, 20.1. HRMS (ESI) m/z calculated for $C_{29}H_{43}ClFN_4O_5S$ $[M+H]^+$: 613.2622; found $[M+H]^+$: 613.2622.

2-(2,6-Dioxo-1,7-diazacyclododecan-1-yl)-N-(pyridin-3-ylmethyl)dodec-11-enamide 6q:



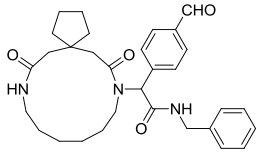
Prepared according to procedure **B** and purified by column chromatography using CH_2Cl_2:MeOH isolated as yellow semisolid (40%, 0.193g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54-8.40 (m, 2H), 7.85 (s, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.28-7.24 (m, 1H), 7.01-6.88 (m, 1H), 5.85-5.68 (m, 1H), 4.98-4.86 (m, 2H), 4.70-4.56 (m, 1H), 4.57-4.44 (m, 1H), 4.26-4.11 (m, 1H), 3.53 (s, 1H), 3.25 (t, *J* = 6.8 Hz, 2H), 2.91 (s, 1H), 2.53-2.44 (m, 1H), 2.32-2.23 (m, 1H), 2.21-2.15 (m, 1H), 2.14- 2.09 (m, 1H), 2.02-1.98 (m, 2H), 1.96-1.88 (m, 2H), 1.71 (s, 1H), 1.54-1.46 (m, 1H), 1.45 -1.39 (m, 2H), 1.38-1.29 (m, 3H), 1.29-1.15 (m, 11H), 1.11-1.01 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.5, 172.8, 171.6, 161.2, 148.7, 148.2, 139.2, 136.2, 123.7, 114.2, 58.7, 44.4, 40.6, 39.7, 34.7, 33.8, 29.7, 29.4, 29.3, 29.2, 29.1, 28.9, 27.8, 26.6, 26.3, 22.3, 21.6. HRMS (ESI) m/z calculated for $C_{28}H_{45}N_4O_3$ $[M+H]^+$: 485.34842; found $[M+H]^+$: 485.34836.

N-Butyl-2-cyclopropyl-2-(5,13-dioxo-7,8,10,11,12,13-hexahydrodibenzo[f,h][1,4,11]-thiadiazacyclotridecin-6(5H)-yl)acetamide 6r:



Prepared according to procedure **C** and purified by column chromatography using CH_2Cl_2:MeOH isolated as yellow semisolid (75%, 0.359g); ^{1}H NMR (500 MHz, $CDCl_3$, 1:1 ratio of atropisomers) δ 7.81-7.76 (m, 1H), 7.75-7.69 (m, 1H), 7.67-7.63 (m, 1H), 7.60-7.55 (m, 1H), 7.53-7.42 (m, 9H), 7.42-7.31 (m, 3H), 6.67-6.60 (m, 1H), 6.27 (t, *J* = 5.4 Hz, 1H), 6.17 (dd, *J* = 7.4, 4.3 Hz, 1H), 6.02 (t, *J* = 6.0 Hz, 1H), 3.92-3.82 (m, 2H), 3.80-3.66 (m, 2H), 3.63-3.40 (m, 3H), 3.38-3.20 (m, 3H), 3.18-2.98 (m, 3H), 2.84-2.68 (m, 3H), 2.66-2.41 (m, 2H), 2.15 (td, *J* = 13.1, 5.0 Hz, 1H), 2.03-1.91 (m, 1H), 1.64-1.53 (m, 1H), 1.50-1.40 (m, 3H), 1.38-1.28 (m, 4H), 1.28-1.17 (m, 4H), 0.93 (t, *J* = 7.2 Hz, 6H), 0.86-0.77 (m, 1H), 0.72-0.56 (m, 2H), 0.44-0.32 (m, 2H), 0.30-0.20 (m, 2H), 0.20-0.30 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$, 1:1 ratio of atropisomers) δ 171.5, 171.4, 170.4, 170.3, 168.3, 167.7, 137.2, 137.1, 137.0, 135.7, 135.5, 135.4, 135.0, 134.5, 132.7, 132.7, 132.3, 131.5, 129.7, 129.4, 128.9, 128.7, 128.3, 128.2, 128.0, 127.9, 127.4, 127.4, 63.9, 62.7, 48.9, 47.6, 42.6, 41.4, 39.1, 33.6, 31.4, 31.3 , 31.3, 31.0, 30.6, 20.1, 20.0, 13.8, 13.7, 10.0, 9.3, 6.3, 6.0, 3.0, 2.9. HRMS (ESI) m/z calculated for $C_{27}H_{34}N_3O_3S$ $[M+H]^+$: 480.23136; found $[M+H]^+$: 480.23126.

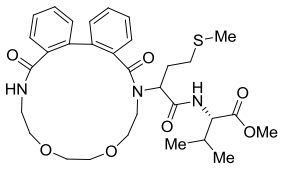
N-Benzyl-2-(7,16-dioxo-8,15-diazaspiro[4.12]heptadecan-8-yl)-2-(4-formylphenyl)-acetamide 6s:



Prepared according to procedure **B** and purified by column chromatography using CH_2Cl_2:MeOH isolated as colorless oil (43%,); ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.00 (s, 1H), 7.88 (d, *J* = 8.2 Hz, 2H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.32-7.28 (m, 4H), 7.28-7.22 (m, 1H), 7.11 (t, *J* = 5.8 Hz, 1H), 6.12 (t, *J* = 5.9 Hz, 1H),

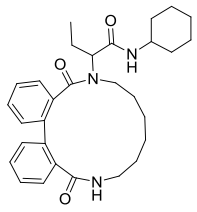
5.01 (s, 1H), 4.56 (dd, *J* = 15.0, 6.0 Hz, 1H), 4.40 (dd, *J* = 15.0, 5.6 Hz, 1H), 3.69-3.51 (m, 2H), 3.08-2.91 (m, 2H), 2.87 (d, *J* = 16.3 Hz, 1H), 2.50 (d, *J* = 12.9 Hz, 1H), 2.35 (d, *J* = 16.2 Hz, 1H), 2.26-2.15 (m, 1H), 2.06 (d, *J* = 12.8 Hz, 1H), 1.99-1.87 (m, 2H), 1.87-1.80 (m, 2H), 1.75-1.58 (m, 6H), 1.54-1.42 (m, 4H), 1.41-1.29 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.4, 173.0, 172.6, 169.2, 141.9, 137.7, 136.4, 130.4, 130.0, 128.6, 127.6, 127.5, 65.1, 45.7, 45.0, 44.1, 43.9, 41.0, 39.1, 38.0, 26.0, 25.8, 24.8, 24.3, 23.6, 22.3; HRMS (ESI) m/z calculated for $C_{31}H_{40}N_3O_4$ $[M+H]^+$: 518.3013; found $[M+H]^+$: 518.3012.

(2*S*)-Methyl 2-(2-(5,16-dioxo-7,8,10,11,13,14,15,16-octahydrodibenzo[i,k][1,4,7,14]-dioxadiazacyclohexadecin-6(5H)-yl)-4-(methylthio)butanamido)-3-methylbutanoate 6t:



Prepared according to procedure **B** and purified by column chromatography using CH_2Cl_2:MeOH isolated as solid (42%, 0.251g); ^{1}H NMR (500 MHz, $CDCl_3$, mixture of 1:1:1:1 ratio of diastereomers and atropisomers) δ 9.21 (d, *J* = 8.8 Hz, 1H), 9.02 (d, *J* = 9.0 Hz, 1H), 8.97 (d, *J* = 8.2 Hz, 1H), 8.89 (d, *J* = 8.4 Hz, 1H), 7.90 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.75 (dd, *J* = 7.9, 1.3 Hz, 1H), 7.74-7.69 (m, 2H), 7.69-7.64 (m, 2H), 7.59-7.50 (m, 4H), 7.50-7.41 (m, 10H), 7.41-7.35 (m, 3H), 7.27-7.23 (m, 1H), 7.20-7.16 (m, 2H), 4.93 (dd, *J* = 10.6, 3.4 Hz, 1H), 4.87 (dd, *J* = 11.0, 3.2 Hz, 1H), 4.77 (dd, *J* = 8.8, 6.0 Hz, 1H), 4.65 (dd, *J* = 8.4, 6.3 Hz, 1H), 4.62-4.55 (m, 2H), 4.54-4.45 (m, 1H), 4.04 (s, 1H), 3.83 (s, 3H), 3.78 (s, 6H), 3.65-3.59 (m, 3H), 3.59-3.50 (m, 6H), 3.44-3.32 (m, 5H), 3.30-3.22 (m, 4H), 3.22-3.15 (m, 3H), 3.09-2.95 (m, 3H), 2.86-2.76 (m, 3H), 2.65-2.54 (m, 3H), 2.52-2.44 (m, 2H), 2.43-2.34 (m, 2H), 2.33-2.23 (m, 4H), 2.09 (s, 6H), 1.96 (s, 3H), 1.75 (s, 2H), 1.12 (d, *J* = 6.9 Hz, 3H), 1.10 (d, *J* = 6.8 Hz, 3H), 1.01 (d, *J* = 7.0 Hz, 3H), 1.00-0.97 (m, 3H), 0.95 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$, mixture of 1:1:1:1 ratio of diastereomers and atropisomers) δ 173.9, 173.4, 172.7, 172.5, 172.4, 171.1, 170.4, 170.1, 169.3, 143.7, 143.5, 139.0, 138.7, 137.6, 137.5, 136.3, 136.1, 132.0, 131.6, 131.2, 131.2, 130.8, 129.8, 128.9, 128.8, 128.8, 128.4, 128.2, 127.9, 127.9, 127.9, 127.8, 127.7, 127.1, 127.1, 127.0, 72.6, 71.8, 71.6, 71.1, 70.7, 70.5, 69.9, 69.8, 68.3, 65.7, 65.4, 63.6, 63.5, 58.6, 58.4, 57.9, 57.5, 57.2, 52.1, 52.1, 52.0, 44.4, 44.0, 39.6, 38.9, 38.8, 31.3, 31.1, 31.1, 30.8, 30.4, 29.9, 29.8, 26.9, 19.4, 19.3, 19.0, 18.8, 18.2, 17.8, 15.3, 15.2, 15.0; HRMS (ESI) m/z calculated for $C_{31}H_{42}N_3O_7S$ $[M+H]^+$: 600.2738; found $[M+H]^+$: 600.2738.

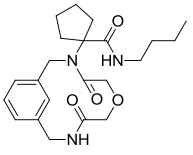
N-Cyclohexyl-2-(5,14-dioxo-7,8,9,10,11,12,13,14-octahydrodibenzo[c,e][1,8]diaza-cyclotetradecin-6(5H)-yl)butanamide 6u:



Prepared according to procedure **C** and purified by column chromatography using CH_2Cl_2:MeOH isolated as solid (41%, 0.200g); ^{1}H NMR (500 MHz, $CDCl_3$, 1:1 ratio of atropisomers) δ 8.01-7.95 (m, 1H), 7.87-7.83 (m, 1H), 7.58-7.54 (m, 1H), 7.52-7.48 (m, 4H), 7.48-7.46 (m, 1H), 7.45 (d, *J* = 2.2 Hz, 1H), 7.44-7.40 (m, 4H), 7.40-7.36 (m, 2H), 7.36-7.31 (m, 1H), 6.68 (d, *J* = 8.4 Hz, 1H), 6.09 (d, *J* = 6.3 Hz, 1H), 5.81 (t, *J* = 5.6 Hz, 1H), 5.58 (t, *J* = 5.7 Hz, 1H), 4.71-4.63 (m, 1H), 4.52-4.43 (m, 1H), 3.72-3.62 (m, 1H), 3.55-3.43 (m, 1H), 3.42-3.32 (m, 1H), 3.28-3.01 (m, 5H), 2.94-2.83 (m, 1H), 2.08 (s, 1H), 2.04-1.95 (m, 1H), 1.85-1.75 (m, 3H), 1.74-1.62 (m, 6H), 1.62-1.52 (m, 5H), 1.52-1.45 (m, 1H), 1.43-1.03 (m, 20H), 0.89 (t, *J* = 7.4 Hz, 3H), 0.71-0.62 (m, 1H), 0.53-0.48 (m, 1H), 0.43 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126

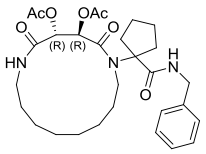
MHz, $CDCl_3$ 1:1 ratio of atropisomers) δ 172.1, 171.9, 170.3, 169.9, 167.6, 167.3, 137.5, 137.2, 137.0, 136.9, 136.4, 135.3, 134.2, 133.5, 133.1, 132.4, 132.0, 131.4, 130.1, 129.8, 129.5, 128.9, 128.9, 128.7, 128.7, 128.4, 128.2, 128.1, 127.8, 59.7, 59.1, 47.9, 47.7, 46.1, 45.1, 39.1, 38.8, 32.8, 32.8, 32.5, 32.5, 27.2, 27.2, 26.8, 26.6, 25.5, 25.4, 24.9, 24.7, 24.6, 24.0, 23.5, 23.2, 22.7, 21.0, 20.4, 10.8, 9.8; HRMS (ESI) m/z calculated for $C_{30}H_{40}N_3O_3$ $[M+H]^+$: 490.3064; found $[M+H]^+$: 490.3065.

N-Butyl-1-{4,8-dioxo-6-oxa-3,9-diazabicyclo[9.3.1]pentadeca-1(14),11(15),12-trien-3-yl}cyclopentane-1-carboxamide 6v:



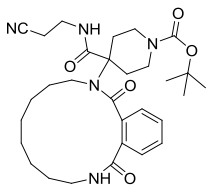
Prepared according to procedure **C** and purified by column chromatography using CH_2Cl_2:MeOH isolated as semi solid (50%, 0.200g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.18 (d, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 6.7 Hz, 1H), 6.96 (d, *J* = 7.5 Hz, 1H), 6.84-6.77 (m, 1H), 4.41 (s, 3H), 3.99 (s, 1H), 3.93 (s, 2H), 3.43 (s, 2H), 3.25-3.18 (m, 2H), 2.69-2.59 (m, 1H), 1.80 (s, 2H), 1.60 (s, 3H), 1.51-1.40 (m, 2H), 1.37-1.25 (m, 2H), 0.88 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.0, 172.9, 171.3, 140.9, 136.7, 129.1, 126.7, 123.4, 74.2, 71.6, 69.5, 49.3, 43.9, 39.5, 36.0, 31.5, 22.8, 20.1, 13.8. HRMS (ESI) m/z calculated for $C_{22}H_{32}N_3O_4$ $[M+H]^+$: 402.2387; found $[M+H]^+$: 402.2386.

(3R,4R)-1-(1-(Benzylcarbamoyl)cyclopentyl)-2,5-dioxo-1,6-diazacyclotetradecane-3,4-diyl diacetate 6w:



Prepared according to procedure **B** and purified by column chromatography using DCM/MeOH (85:15) isolated as colorless oil (26%, 0.141g); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.27 (m, 8H), 7.24-7.18 (m, 2H), 6.91-6.83 (m, 2H), 6.46-6.36 (m, 2H), 5.70 (dd, *J* = 7.8, 3.4 Hz, 2H), 5.62 (t, *J* = 3.8 Hz, 2H), 4.45-4.36 (m, 2H), 4.36-4.29 (m, 2H), 3.49- 3.30 (m, 5H), 3.25-3.16 (m, 3H), 2.60 (s, 2H), 2.45-2.34 (m, 2H), 2.17 (s, 6H), 1.99 (s, 6H), 1.95-1.87 (m, 4H), 1.85-1.78 (m, 10H), 1.71-1.65 (m, 4H), 1.56-1.50 (m, 4H), 1.40- 1.32 (m, 14H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 174.4, 170.7, 170.6, 169.4, 169.4, 167.5, 167.4, 166.2, 165.9, 139.2, 139.2, 128.3, 127.6, 127.5, 126.8, 126.7, 73.6, 70.9, 70.7, 70.7, 70.5, 46.0, 45.8, 43.6, 39.4, 39.2, 36.2, 36.2, 36.1, 30.6, 29.8, 29.4, 29.1, 29.0, 28.3, 28.0, 26.8, 26.2, 26.1, 26.0, 24.6, 24.6, 24.5, 24.5, 20.7, 20.4, 20.3; HRMS (ESI) m/z calculated for $C_{29}H_{42}N_3O_7$ $[M+H]^+$: 544.3017; found $[M+H]^+$: 544.3016.

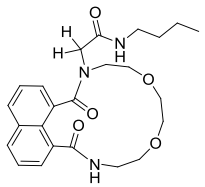
***tert*-Butyl 4-((2-cyanoethyl)carbamoyl)-4-(1,12-dioxo-3,4,5,6,7,8,9,10,11,12-decahydrobenzo[c][1,6]diazacyclotetradecin-2(1H)-yl)piperidine-1-carboxylate 6x:**



Prepared according to procedure **B** and purified by column chromatography using CH_2Cl_2:MeOH isolated as semi-solid (32%, 0.177g); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.67 (d, *J* = 8.1, 1.1 Hz, 1H), 7.56 (t, *J* = 7.5, 1.1 Hz, 1H), 7.45 (t, *J* = 7.7, 1.3 Hz, 1H), 7.19 (d, *J* = 7.6, 1.3 Hz, 1H), 6.49 (s, 1H), 4.20-4.07 (m, 1H), 3.95-3.85 (m, 1H), 3.69-3.50 (m, 3H), 3.42 (s, 1H), 3.17-3.08 (m, 1H), 3.08-3.01 (m, 1H), 2.93 (t, *J* = 13.6 Hz, 1H), 2.84-2.75 (m, 1H),

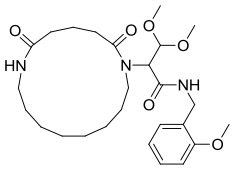
2.72-2.64 (m, 1H), 2.64-2.55 (m, 1H), 2.25-2.17 (m, 1H), 2.10-1.99 (m, 2H), 1.83-1.74 (m, 1H), 1.72-1.65 (m, 1H), 1.65-1.56 (m, 1H), 1.48 (s, 9H), 1.44-1.08 (m, 9H), 0.90-0.77 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.2, 172.7, 165.7, 154.9, 138.7, 132.3, 129.0, 127.9, 126.0, 118.6, 79.7, 63.6, 60.4, 48.0, 41.8, 40.5, 39.4, 36.5, 36.3, 32.9, 31.3, 28.7, 28.5, 26.5, 26.0, 23.2, 21.8, 20.4, 17.1; HRMS (ESI) m/z calculated for $C_{30}H_{43}N_5NaO_5$ $[M+H]^+$: 576.3156; found $[M+H]^+$: 576.3155.

N-Butyl-2-(1,12-dioxo-3,4,6,7,9,10,11,12-octahydronaphtho[1,8-ij][1,4,7,13]dioxadiazacyclopentadecin-2(1H)-yl)acetamide 6y:



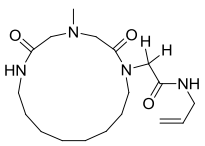
Prepared according to procedure **C** and purified by column chromatography using CH_2Cl_2:MeOH isolated as colorless oil (22%, 0.097g); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (d, *J* = 7.2 Hz, 2H), 8.23 (d, *J* = 8.2 Hz, 2H), 7.77 (t, *J* = 7.4 Hz, 2H), 4.45 (t, *J* = 6.1 Hz, 2H), 3.82 (t, *J* = 6.1 Hz, 2H), 3.75-3.66 (m, 5H), 3.63-3.54 (m, 3H), 3.48 (s, 2H), 3.28-3.19 (m, 2H), 1.55-1.39 (m, 2H), 1.30 (s, 2H), 0.88 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.4, 164.2, 134.1, 131.6, 131.3, 128.2, 127.0, 122.5, 70.1, 69.4, 68.8, 68.0, 53.0, 52.6, 49.0, 39.1, 31.6, 20.0, 13.8; HRMS (ESI) m/z calculated for $C_{24}H_{32}N_3O_5$ $[M+H]^+$: 442.2342; found $[M+H]^+$:442.2336.

2-(2,6-Dioxo-1,7-diazacyclopentadecan-1-yl)-3,3-dimethoxy-N-(2-methoxybenzyl)-propanamide 6z:



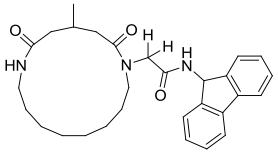
Prepared according to procedure A and purified by column chromatography using CH_2Cl_2:MeOH isolated as solid (46%, 0.226g); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.23 (m, 2H), 6.95-6.88 (m, 2H), 5.45 (s, 1H), 5.07 (d, *J* = 7.9 Hz, 1H), 4.63 (s, 1H), 4.49 (dd, *J* = 14.6, 6.5 Hz, 1H), 4.38 (dd, *J* = 14.6, 5.4 Hz, 1H), 3.90 (s, 3H), 3.46 (s, 3H), 3.42-3.34 (m, 1H), 3.32 (s, 3H), 3.31-3.26 (m, 1H), 3.26-3.20 (m, 2H), 2.44-2.35 (m, 1H), 2.34-2.27 (m, 1H), 2.24-2.14 (m, 2H), 2.10-1.98 (m, 2H), 1.61-1.50 (m, 2H), 1.50- 1.41 (m, 1H), 1.41-1.18 (m, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 172.6, 168.3, 157.6, 129.5, 128.6, 126.4, 120.5, 110.2, 101.5, 55.6, 55.3, 53.2, 47.7, 39.3, 38.1, 35.3, 31.6, 28.4, 27.3, 26.0, 24.6, 23.9, 20.4; HRMS (ESI) m/z calculated for $C_{26}H_{41}N_3NaO_6$ $[M+Na]^+$: 514.2888; found $[M+Na]^+$: 514.2884.

N-allyl-2-(4-methyl-2,6-dioxo-1,4,7-triazacyclopentadecan-1-yl)acetamide 6aa:



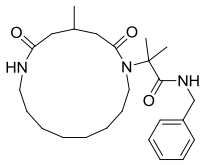
Prepared according to procedure **C** and purified by column chromatography using CH_2Cl_2:MeOH isolated as solid (41%, 0.144g); ^{1}H NMR (500 MHz, $CDCl_3$, rotamers were obsorved) δ 7.76 (s, 1H), 6.91 (t, *J* = 6.1 Hz, 1H), 6.70 (t, *J* = 5.6 Hz, 1H), 6.60-6.45 (m, 1H), 5.90-5.73 (m, 2H), 5.23-5.07 (m, 4H), 3.98 (s, 2H), 3.97 (s, 2H), 3.95-3.89 (m, 2H), 3.88-3.81 (m, 2H), 3.61-3.51 (m, 2H), 3.41 (s, 2H), 3.40-3.33 (m, 4H), 3.33-3.28 (m, 2H), 3.25 (s, 2H), 3.21 (s, 4H), 2.52 (s, 3H), 2.44 (s, 3H), 1.67-1.53 (m, 6H), 1.53 – 1.45 (m, 2H), 1.45-1.29 (m, 13H), 1.24-1.14 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, rotamers were obsorved) δ 171.1, 170.8, 170.4, 169.8, 169.0, 167.7, 133.8, 133.6, 117.0, 116.3, 61.2, 60.8, 59.3, 58.1, 51.0, 50.0, 49.7, 45.5, 44.7, 44.2, 42.0, 41.8, 38.6, 37.2, 27.7, 27.3, 26.7, 26.2, 25.9, 25.9, 25.3, 24.8, 23.9, 23.3, 23.1, 23.0; HRMS (ESI) m/z calculated for $C_{18}H_{33}N_4O_3$ $[M+H]^+$: 353.2547; found $[M+H]^+$: 353.2545.

N-(9H-Fluoren-9-yl)-2-(4-methyl-2,6-dioxo-1,7-diazacyclopentadecan-1-yl)acetamide 6ab: Prepared according to procedure **B** and purified by column chromatography using



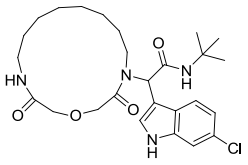
CH_2Cl_2:MeOH isolated as solid (27%, 0.128g); ^{1}H NMR (500 MHz, $CDCl_3$+Methanol-d_4) δ 7.70-7.54 (m, 2H), 7.53-7.40 (m, 2H), 7.39 -7.26 (m, 3H), 7.26-7.16 (m, 2H), 6.19-6.03 (m, 1H), 5.34 -5.17 (m, 1H), 3.99 (h, *J* = 6.5, 5.1 Hz, 2H), 3.42-3.23 (m, 3H), 3.23-3.09 (m, 2H), 2.93- 2.74 (m, 1H), 2.42-2.26 (m, 2H), 2.26-2.05 (m, 3H), 1.97-1.75 (m, 1H), 1.42-1.36 (m, 2H), 1.32-1.12 (m, 8H), 1.00-0.88 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$+Methanol-d_4) δ 172.9, 172.4, 170.6, 144.0, 140.6, 128.4, 127.5, 124.9, 119.7, 119.7, 54.6, 50.8, 49.9, 42.5, 41.2, 38.5, 37.9, 37.5, 28.7, 27.5, 26.1, 26.1, 25.1, 23.7, 23.7, 20.5; HRMS (ESI) m/z calculated for $C_{29}H_{38}N_3O_3$ $[M+H]^+$: 476.2908; found $[M+H]^+$: 476.2907.

N-Benzyl-2-methyl-2-(4-methyl-2,6-dioxo-1,7-diazacyclopentadecan-1-yl)propanamide 6ac:



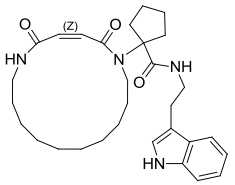
Prepared according to procedure **B** and purified by column chromatography using CH_2Cl_2:MeOH isolated as solid (32%, 0.137g); ^{1}H NMR (500 MHz, Chloroform-d) δ 7.29 (s, 1H), 7.27-7.22 (m, 4H), 7.20-7.15 (m, 1H), 4.46-4.15 (m, 2H), 3.63-3.53 (m, 1H), 3.31-3.27 (m, 1H), 3.24-3.16 (m, 1H), 3.16-3.07 (m, 1H), 2.91 (dt, *J* = 13.8, 4.5 Hz, 1H), 2.44-2.32 (m, 1H), 2.32-2.18 (m, 2H), 2.09 (dd, *J* = 15.8, 7.9 Hz, 1H), 1.88 (dd, *J* = 13.4, 7.9 Hz, 1H), 1.80-1.64 (m, 1H), 1.52-1.46 (m, 3H), 1.45 (s, 3H), 1.42 (s, 3H), 1.41-1.38 (m, 2H), 1.33-1.17 (m, 5H), 1.01 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, Chloroform-d) δ 176.0, 172.4, 172.2, 139.0, 128.3, 127.6, 126.9, 62.0, 44.4, 43.4, 42.5, 39.5, 37.2, 29.4, 28.8, 27.4, 26.1, 25.0, 25.0, 24.0, 23.6, 23.2, 20.6; HRMS (ESI) m/z calculated for $C_{25}H_{40}N_3O_3$ $[M+H]^+$: 452.2884; found $[M+H]^+$: 452.2882.

N-(tert-Butyl)-2-(6-chloro-1H-indol-3-yl)-2-(3,14-dioxo-1-oxa-4,13-diazacyclopentadecan-4-yl)acetamide 6ad:



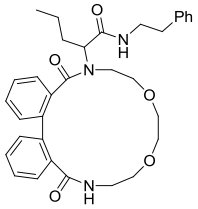
Prepared according to procedure **B** and purified by column chromatography using CH_2Cl_2:MeOH isolated as solid (15%, 0.076g); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.48 (s, 1H), 7.70 (d, *J* = 2.5 Hz, 1H), 7.46-7.38 (m, 2H), 7.14 (dd, *J* = 8.5, 1.8 Hz, 1H), 6.51-6.39 (m, 1H), 6.21 (s, 1H), 6.06 (s, 1H), 4.44-4.27 (m, 2H), 4.17 (s, 2H), 3.44-3.32 (m, 2H), 3.26-3.15 (m, 1H), 3.13-3.01 (m, 1H), 1.69-1.56 (m, 7H), 1.36 (s, 11H), 1.26-1.21 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.9, 168.8, 168.6, 136.1, 128.8, 126.6, 125.5, 121.2, 119.4, 111.4, 109.5, 70.9, 70.1, 54.4, 51.5, 45.6, 37.8, 28.6, 28.2, 27.2, 25.5, 25.2, 23.7, 23.1; HRMS (ESI) m/z calculated for $C_{26}H_{38}ClN_4O_4$ $[M+H]^+$: 504.2576; found $[M+H]^+$: 505.2576.

(Z)-N-(2-(1H-Indol-3-yl)ethyl)-1-(2,5-dioxo-1,6-diazacyclohexadec-3-en-1-yl)cyclopentanecarboxamide 6ae:



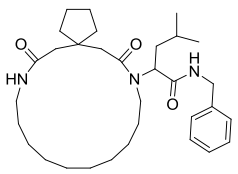
Prepared according to procedure **C** and purified by column chromatography using CH_2Cl_2:MeOH isolated as white solid (47%, 0.237g). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.73 (s, 1H), 8.54-8.50 (m, 1H), 8.24-8.20 (m, 1H), 7.54 (d, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.14-6.98 (m, 2H), 6.93 (dd, *J* = 11.0, 3.9 Hz, 1H), 6.54 (d, *J* = 11.8 Hz, 1H), 6.00 (d, *J* = 11.9 Hz, 1H), 3.74-3.67 (m, 1H), 3.48-3.43 (m, 2H), 3.18-3.15 (m, 2H), 2.98-2.83 (m, 3H), 2.75- 2.66 (m, 1H), 2.04-1.94 (m, 1H), 1.94-1.84 (m, 1H), 1.82-1.72 (m, 2H), 1.67-1.51 (m, 5H), 1.37-1.30 (m, 2H), 1.29-1.21 (m, 6H), 1.18-1.10 (m, 3H), 1.08-1.03 (m, 1H), 0.98- 0.89 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 179.7, 173.3, 169.2, 142.2, 141.4, 132.5, 128.5, 127.5, 126.0, 123.3, 123.2, 117.4, 116.6, 84.3, 76.8, 51.7, 45.5, 43.1, 42.3, 40.8, 33.8, 31.5, 31.4, 30.9, 30.8, 30.5, 29.8, 29.7, 29.4, 28.4. HRMS (ESI) m/z calculated for $C_{30}H_{43}N_4O_3$ $[M+H]^+$: 507.3329; found $[M+H]^+$: 507.3330.

2-(5,16-Dioxo-7,8,10,11,13,14,15,16-octahydrodibenzo[i,k][1,4,7,14]dioxadiazacyclohexadecin-6(5H)-yl)-N-phenethyl pentanamide 6af:



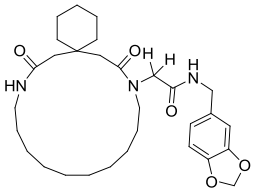
Prepared according to procedure **B** and purified by column chromatography using CH_2Cl_2:MeOH isolated as solid (37%, 0.206g); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.06 (d, *J* = 8.7 Hz, 1H), 8.77 (t, *J* = 5.6 Hz, 1H), 7.63 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.46-7.40 (m, 3H), 7.38-7.32 (m, 4H), 7.31-7.25 (m, 4H), 7.23-7.19 (m, 1H), 7.02 (dd, *J* = 7.6, 1.2 Hz, 1H), 4.61 (dd, *J* = 11.7, 3.2 Hz, 1H), 4.47-4.35 (m, 1H), 3.84-3.73 (m, 1H), 3.71-3.58 (m, 2H), 3.53-3.46 (m, 1H), 3.44-3.38 (m, 3H), 3.20-3.15 (m, 1H), 3.11- 3.03 (m, 1H), 2.99-2.92 (m, 5H), 2.31-2.21 (m, 1H), 2.21-2.14 (m, 1H), 1.62-1.49 (m, 1H), 1.30-1.13 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4, 170.5, 169.3, 143.6, 139.3, 138.9, 137.5, 131.9, 131.3, 131.1, 128.6, 128.6, 128.5, 127.9, 127.7, 127.3, 126.8, 126.5, 72.4, 70.7, 69.8, 65.8, 65.2, 43.9, 40.6, 38.7, 35.3, 32.2, 20.3, 13.9; HRMS (ESI) m/z calculated for $C_{33}H_{39}N_3NaO_5$ $[M+Na]^+$: 580.2782; found $[M+H]^+$: 580.5779.

N-Benzyl-2-(7,20-dioxo-8,19-diazaspiro[4.16]henicosan-8-yl)-4-methylpentanamide 6ag:



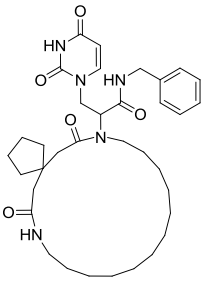
Prepared according to procedure **B** and purified by column chromatography using CH_2Cl_2:MeOH isolated as white solid (47%, 0.246g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (t, *J* = 5.9 Hz, 1H), 7.30 (d, *J* = 7.3 Hz, 2H), 7.21 (t, *J* = 7.5 Hz, 2H), 7.16-7.12 (m, 1H), 5.95- 5.81 (m, 1H), 4.41 (dd, *J* = 14.5, 6.3 Hz, 1H), 4.23 (dd, *J* = 14.5, 5.7 Hz, 1H), 3.35-3.15 (m, 2H), 2.98-2.76 (m, 2H), 2.59-2.51 (m, 1H), 2.48 (d, *J* = 16.1 Hz, 1H), 2.23 (d, *J* = 16.1 Hz, 1H), 2.08-2.01 (m, 1H), 1.84-1.75 (m, 1H), 1.67-1.56 (m, 8H), 1.50-1.41 (m, 3H), 1.40-1.34 (m, 2H), 1.33-1.28 (m, 2H), 1.28-1.12 (m, 12H), 0.90 (d, *J* = 3.0 Hz, 3H), 0.88 (d, *J* = 2.8 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 172.3, 172.0, 139.5, 128.1, 126.6, 55.7, 46.2, 44.0, 43.5, 41.3, 39.6, 39.5, 38.9, 36.7, 28.8, 27.0, 26.8, 26.7, 25.9, 25.3, 24.9, 24.7, 24.4, 24.1, 23.8, 23.4, 21.8. HRMS (ESI) m/z calculated for $C_{32}H_{52}N_3O_3$ $[M+H]^+$: 526.4003; found $[M+H]^+$: 526.4002.

N-(Benzo[d][1,3]dioxol-5-ylmethyl)-2-(8,21-dioxo-9,20-diazaspiro[5.16]docosan-9-yl)acetamide 6ah:



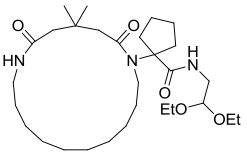
Prepared according to procedure **B** and purified by column chromatography using CH_2Cl_2:MeOH isolated as white solid (47%, 0.247g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (t, *J* = 5.6 Hz, 1H), 6.84 (d, *J* = 1.3 Hz, 1H), 6.81 – 6.72 (m, 1H), 6.66 (d, *J* = 7.9 Hz, 1H), 5.86 (s, 2H), 5.81 (t, *J* = 6.1 Hz, 1H), 4.26 (d, *J* = 5.9 Hz, 2H), 4.07-3.99 (m, 2H), 3.25-3.12 (m, 2H), 3.14-2.99 (m, 2H), 2.40 (s, 2H), 2.27 (s, 2H), 1.79 (s, 1H), 1.64-1.56 (m, 2H), 1.53-1.35 (m, 12H), 1.34-1.16 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.0, 171.9, 169.5, 147.4, 146.4, 133.3, 121.4, 109.0, 107.9, 100.8, 51.8, 51.6, 43.2, 43.0, 39.5, 39.0, 37.6, 35.7, 28.4, 27.0, 26.9, 26.6, 26.1, 24.7, 24.6, 24.3, 23.8, 21.7. HRMS (ESI) m/z calculated for $C_{30}H_{46}N_3O_5$ $[M+H]^+$: 528.3432; found $[M+H]^+$: 528.34314.

N-Benzyl-3-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-2-(7,22-dioxo-8,21-diaza-spiro[4.18]tricosan-8-yl)propanamide 6ai:



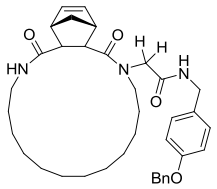
Prepared according to procedure **B** and purified by column chromatography using CH_2Cl_2:MeOH isolated as solid (29%, 0.180g); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.61 (s, 1H), 8.38 (t, *J* = 6.0 Hz, 1H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.30-7.21 (m, 5H), 7.20-7.15 (m, 1H), 5.64 (dd, *J* = 8.0, 2.1 Hz, 1H), 5.57 (dd, *J* = 7.9, 4.4 Hz, 1H), 4.61 (dd, *J* = 13.9, 7.1 Hz, 1H), 4.41 (dd, *J* = 14.7, 6.4 Hz, 1H), 4.28 (dd, *J* = 14.8, 5.6 Hz, 1H), 4.19-4.13 (m, 1H), 4.01-3.92 (m, 1H), 3.45-3.33 (m, 2H), 3.32-3.22 (m, 1H), 2.75-2.64 (m, 2H), 2.42 (d, *J* = 12.9 Hz, 1H), 2.13- 2.06 (m, 2H), 2.02-1.88 (m, 1H), 1.85-1.75 (m, 1H), 1.67-1.49 (m, 8H), 1.46-1.40 (m, 2H), 1.35-1.26 (m, 14H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7, 172.2, 170.2, 164.3, 151.3, 147.2, 139.0, 128.1, 127.9, 126.7, 101.0, 61.6, 51.2, 50.7, 43.5, 43.3, 43.0, 41.0, 39.5, 39.4, 39.0, 28.3, 27.5, 27.4, 27.1, 26.9, 26.8, 26.6, 26.0, 25.6, 24.8, 24.2, 23.5; HRMS (ESI) m/z calculated for $C_{35}H_{52}N_5O_5$ $[M+H]^+$: 622.3963; found $[M+H]^+$: 622.3963.

N-(2,2-Diethoxyethyl)-1-(4,4-dimethyl-2,6-dioxo-1,7-diazacycloheptadecan-1-yl)-cyclopentanecarboxamide 6aj:



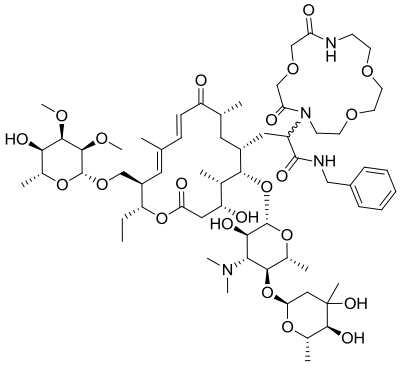
Prepared according to procedure **B** and purified by column chromatography using CH_2Cl_2:MeOH isolated as white solid (39%, 0.203g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (s, 1H), 5.96 (s, 1H), 4.62 (t, *J* = 5.6 Hz, 1H), 3.77-3.63 (m, 2H), 3.61-3.49 (m, 2H), 3.28- 3.16 (m, 6H), 2.49 (s, 2H), 2.32 (s, 4H), 1.88-1.73 (m, 6H), 1.70-1.59 (m, 2H), 1.52-1.46 (m, 2H), 1.44-1.38 (m, 4H), 1.37-1.29 (m, 8H), 1.21 (t, *J* = 7.1 Hz, 6H), 1.15 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.8, 172.6, 172.1, 100.5, 72.5, 61.7, 46.2, 45.7, 42.9, 41.8, 39.0, 36.8, 33.6, 30.0, 29.0, 28.8, 27.1, 26.8, 25.7, 25.4, 25.0, 24.8, 24.4, 15.4. HRMS (ESI) m/z calculated for $C_{29}H_{54}N_3O_5$ $[M+H]^+$: 546.38909; found $[M+H]^+$: 546.38928.

N-(4-(Benzyloxy)benzyl)-2-((17S,20R)-1,16-dioxo-3,4,5,6,7,8,9,10,11,12,13,14,15,16,-16a,17,20,20a-octadecahydro-17,20-methanobenzo[c][1,6]diazacyclooctadecin-2(1H)-yl)acetamide 6ak:



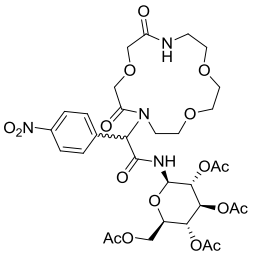
Prepared according to procedure **C** and purified by column chromatography using CH_2Cl_2:MeOH isolated as semi-solid (36%, 0.215g); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43-7.39 (m, 2H), 7.39-7.34 (m, 2H), 7.34-7.31 (m, 1H), 7.26 (t, *J* = 5.9 Hz, 1H), 7.17-7.11 (m, 2H), 6.93-6.88 (m, 2H), 6.08 (dt, *J* = 3.9, 1.8 Hz, 1H), 5.02 (s, 2H), 4.33 (d, *J* = 5.8 Hz, 2H), 3.36 (qt, *J* = 3.4, 2.0 Hz, 1H), 3.34-3.27 (m, 1H), 3.23-3.18 (m, 1H), 3.16 (s, 2H), 2.57- 2.43 (m, 1H), 1.72 (dt, *J* = 8.7, 1.8 Hz, 1H), 1.57-1.49 (m, 1H), 1.42 (td, *J* = 16.0, 15.1, 8.5 Hz, 3H), 1.31-1.12 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.8, 170.2, 158.2, 136.9, 134.4, 130.5, 129.0, 128.6, 128.0, 127.4, 115.1, 70.0, 59.1, 56.4, 52.2, 45.7, 44.9, 42.7, 38.5, 29.5, 29.5, 29.5, 29.5, 29.1, 27.8, 27.4, 27.3, 26.9; HRMS (ESI) m/z calculated for $C_{37}H_{50}N_3O_4$ $[M+H]^+$: 600.3796; found $[M+H]^+$: 600.3782.

N-Benzyl-3-((4R,5S,6S,7R,9R,11E,13E,15R,16R)-6-(((2R,3R,4R,5S,6R)-5-(((2S,5S,-6S)-4,5-dihydroxy-4,6-dimethyltetrahydro-2H-pyran-2-yl)oxy)-4-(dimethylamino)-3-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-16-ethyl-4-hydroxy-15-((((2R,-3R,4R,5R,6R)-5-hydroxy-3,4-dimethoxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-methyl)-5,9,13-trimethyl-2,10-dioxooxacyclohexadeca-11,13-dien-7-yl)-2-(8,12-dioxo-1,4,10-trioxa-7,13-diazacyclopentadecan-7-yl)propanamide 6al:



Prepared according to procedure **B** and purified by column chromatography using CH_2Cl_2:MeOH isolated as solid (53%, 0.677g); ^{1}H NMR (500 MHz, Chloroform-d, major diastereomer) δ 7.86-7.72 (m, 1H), 7.31-7.27 (m, 3H), 7.25-7.18 (m, 2H), 7.10 (t, *J* = 5.7 Hz, 1H), 6.25 (d, *J* = 15.4 Hz, 1H), 5.90 (d, *J* = 10.5 Hz, 1H), 4.95-4.88 (m, 2H), 4.60 (d, *J* = 14.3 Hz, 1H), 4.54 (d, *J* = 7.7 Hz, 1H), 4.49 (dd, *J* = 14.4, 6.5 Hz, 1H), 4.44 (d, *J* = 14.3 Hz, 1H), 4.27-4.15 (m, 4H), 4.04-3.93 (m, 4H), 3.76-3.72 (m, 1H), 3.59 (s, 4H), 3.57-3.50 (m, 4H), 3.45 (s, 4H), 3.42- 3.36 (m, 3H), 3.34-3.24 (m, 5H), 3.20-3.12 (m, 4H), 3.02 (dd, *J* = 7.9, 2.9 Hz, 1H), 2.96- 2.88 (m, 3H), 2.79-2.71 (m, 1H), 2.50-2.45 (m, 2H), 2.44 (s, 6H), 2.43-2.37 (m, 2H), 2.35-2.21 (m, 3H), 2.06-1.93 (m, 2H), 1.88-1.80 (m, 2H), 1.71 (dd, *J* = 14.3, 3.9 Hz, 1H), 1.65-1.49 (m, 4H), 1.25 (dd, *J* = 11.3, 5.6 Hz, 6H), 1.21 (s, 3H), 1.19 (d, *J* = 6.8 Hz, 3H), 0.99 (d, *J* = 5.5 Hz, 3H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$, major diastereomer) δ 204.0, 173.7, 171.7, 170.4, 148.0, 143.2, 138.2, 134.6, 128.5, 128.3, 127.6, 127.3, 117.9, 102.7, 101.2, 96.5, 81.8, 79.9, 77.3, 75.0, 74.9, 73.0, 72.7, 71.9, 70.8, 70.5, 69.9, 69.7, 69.7, 69.4, 69.1, 68.6, 68.3, 67.5, 66.7, 65.9, 61.8, 59.6, 53.5, 45.1, 45.1, 43.9, 41.9, 41.1, 40.8, 40.1, 38.7, 33.1, 32.6, 25.4, 25.1, 18.3, 18.2, 17.8, 17.6, 12.9, 9.6, 9.3; HRMS (ESI) m/z calculated for $C_{64}H_{103}N_4O_{22}$ $[M+H]^+$: 1279.7058; found $[M+H]^+$: 1279.7065.

(2R,3R,4S,5R,6R)-2-(Acetoxymethyl)-6-(2-(8,12-dioxo-1,4,10-trioxa-7,13-diaza-cyclopentadecan-7-yl)-2-(4-nitrophenyl)acetamido)tetrahydro-2H-pyran-3,4,5-triyl triacetate 6am:



Prepared according to procedure **B** and purified by column chromatography using CH_2Cl_2:MeOH isolated as semi-solid (22%, 0.166g); ^{1}H NMR (500 MHz, $CDCl_3$, **2:1 ratio of diastereomers, major isomer**) δ 8.25 (d, *J* = 8.6 Hz, 2H), 7.95-7.89 (m, 1H), 7.82- 7.75 (m, 1H), 7.47 (d, *J* = 8.7 Hz, 2H), 6.21 (s, 1H), 5.54-5.45 (m, 2H), 5.29-5.22 (m, 2H), 4.91 (d, *J* = 14.4 Hz, 1H), 4.38 (d, *J* = 16.4 Hz, 1H), 4.27-4.22 (m, 1H), 4.16-4.09 (m, 2H), 3.95 (d, *J* = 16.2 Hz, 1H), 3.90-3.84 (m, 4H), 3.75-3.69 (m, 2H), 3.63-3.60 (m, 2H), 3.54-3.46 (m, 2H), 3.35- 3.29 (m, 2H), 2.74 (d, *J* = 15.4 Hz, 1H), 2.20 (s, 3H), 2.12 (s, 3H), 2.08 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 170.4, 169.7, 169.7, 169.6, 167.7, 147.9, 141.0, 131.2, 124.1, 78.5, 72.7, 70.9, 70.7, 69.8, 69.6, 68.7, 67.5, 67.5, 67.3, 64.8, 61.8, 60.8, 43.8, 38.5, 20.9, 20.7, 20.6, 20.5; ^{1}H NMR (500 MHz, $CDCl_3$, **2:1 ratio of diastereomers, minor isomer**) δ 8.17 (d, *J* = 8.7 Hz, 2H), 7.95-7.89 (m, 1H), 7.82-7.75 (m, 1H), 7.62 (d, *J* = 8.7 Hz, 2H), 6.21 (s, 1H), 5.45-5.35 (m, 2H), 5.22-5.13 (m, 2H), 4.90 – 4.79 (m, 1H), 4.35 (d, *J* = 16.4 Hz, 1H), 4.22-4.17 (m, 1H), 4.09-4.05 (m, 2H), 3.95 (d, *J* = 16.2 Hz, 1H), 3.84-3.78 (m, 4H), 3.69-3.65 (m, 2H), 3.59-3.54 (m, 2H), 3.45-3.41 (m, 2H), 3.29-3.21 (m, 2H), 2.74 (d, *J* = 15.4 Hz, 1H), 2.23 (s, 3H), 2.13 (s, 3H), 2.06 (s, 3H), 2.02 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.5, 170.4, 169.7, 169.7, 169.4, 168.7, 147.6, 141.2, 130.9, 123.3, 78.2, 72.6, 71.2, 71.0, 70.0, 69.3, 68.9, 67.6, 67.5, 67.4, 67.2, 66.3, 61.8, 61.1, 47.9, 38.8, 21.1, 20.7, 20.6, 20.5; HRMS (ESI) m/z calculated for $C_{32}H_{43}N_4O_{17}$ $[M+H]^+$: 755.2618; found $[M+H]^+$: 755.2617.

Crystal structure determination:

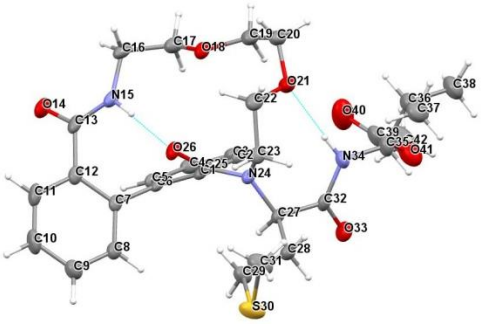
X-ray diffraction data for single crystals of compounds **6i, 6o, 6t, 6z** and **6ad** were collected using SuperNova (Rigaku - Oxford Diffraction) four circle diffractometer with a mirror monochromator and a microfocus MoKα radiation source (λ = 0.7107 Å) for **6i**, **6t** and **6ad** and CuKα radiation source (λ = 1.5418 Å) for **6o** and **6z.** Additionally, the diffractometer was equipped with a CryoJet HT cryostat system (Oxford Instruments) allowing low temperature experiments. Single crystals were mounted on Micro MountsTM. Intensities were collected at 120-130 K. The obtained data sets were processed with CrysAlisPro software.[28] The phase problem was solved by direct methods using SHELXS[29] or SUPERFLIP.[30] Parameters of obtained models were refined by full-matrix least-squares on F^2 using SHELXL-2014/6.[29] Calculations were performed using WinGX integrated system (ver. 2013.2).[31] Figures were prepared with Mercury 3.5 software.[32]

All non-hydrogen atoms in the crystal structures of **6i, 6o, 6t, 6z** and **6ad** were refined anisotropically to ensure the convergence of the refinement process. All hydrogen atoms attached to carbon atoms were positioned with the idealised geometry and refined using the riding model with the isotropic displacement parameter $U_{iso}[H] = 1.2$ (or 1.5) $U_{eq}[C]$. The position of hydrogen atoms linked to the N atoms were found on the difference Fourier map and refined with no restrains on the isotropic displacement parameter. Crystal data and

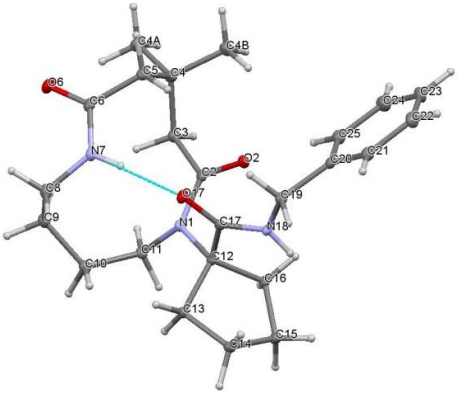
structure refinement results for compounds **6i, 6o, 6t, 6z** and **6ad** are shown in Table 7. Molecular geometry of compounds **6i, 6o, 6t, 6z** and **6ad** observed in the crystal structures are shown in Figure 4.

In the crystal structure of compound **6o** a partial, conformational disorder was observed for cyclopentane fragment. The two alternative conformations were modelled with 64% and 36% refined occupancies for components A and B, respectively. Additionally, voids observed in the crystal lattice are filled with disordered water molecule. Due to high disorder observed of the solvent, hydrogen atoms were not included into the final model. In the crystal structure of compound **6z** a solvent accessible voids are observed (119 $Å^3$), however the Fourier difference map does not indicate solvent position in the crystal lattice.

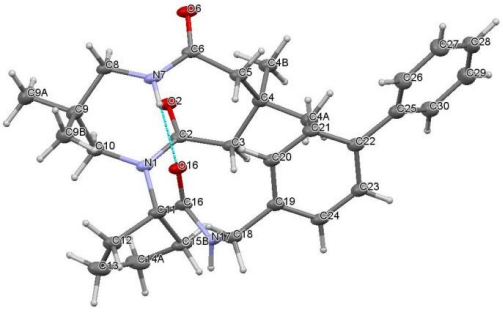
Crystallographic data for structures presented in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 1507159 (**6t**), CCDC 1508125 (**6i**), CCDC 1508127 (**6o**), CCDC 1508126 (**6z**) and CCDC 1547917 (**6ad**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail:deposit@ccdc.cam.ac.uk).



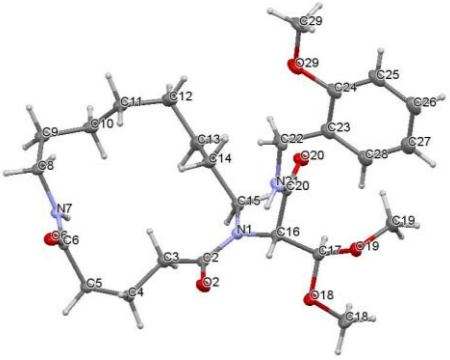
6t



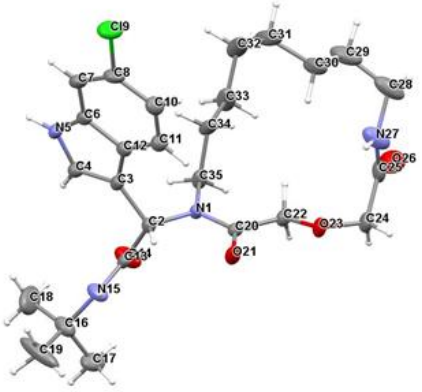
6i



6o



6z



6ad

Figure 4. Molecular geometry observed in the crystal structures of compounds **6i, 6o, 6t, 6z** and **6ad**, showing the atom labelling scheme. For the crystal structure of compound **6o** a conformational disorder is observed and only the more abundant conformer is shown here. The disordered solvent molecules in the asymmetric unit of **6o** was removed for clarity of this figure. For molecules **6i, 6o** and **6t**, the intramolecular hydrogen bond formation is shown with the light-blue, dashed line. Displacement ellipsoids of non-hydrogen atoms are drawn at the 30% probability level. H atoms are presented as small spheres with an arbitrary radius.

Table 7. Crystal data and structure refinement results for compounds **6i, 6o, 6t, 6z** and **6ad**.

	6i	**6o**	**6t**	**6z**	**6ad**
Empirical moiety formula	$C_{24}H_{35}N_3O_3$	$C_{31}H_{41}N_3O_3$, H_2O	$C_{31}H_{41}N_3O_7S$	$C_{26}H_{41}N_3O_6$	$C_{26}H_{37}ClN_4O_4$
Formula weight [g/mol]	413.55	519.61	599.73	491.62	505.05
Temperature [K]	130 (2)	130(2)	119.9 (10)	130(2) K	130 K
Wavelength [Å]	0.7107	1.5418	0.7107	1.5418	0.7107
Crystal system	Monoclinic	Orthorhombic	Monoclinic	Orthorhombic	Hexagonal
Space group	C*c*	P *c c n*	$P2_1/c$	P *b c a*	$P6_1$
Unite cell dimensions	a=14.0931(5) Å b=13.557(4) Å c=12.0951(5) Å α=90° β=108.895(4)° γ=90°	a=27.6390(8) Å b=17.7059(5) Å c= 12.3033(3) Å α=90° β= 90° γ=90°	a=11.5868(3) Å b=14.9472(4) Å c=17.5410(7) Å α= 90.0° β=91.091(3)° γ=90.0°	a=13.252(2) Å b=8.5410(8) Å c= 49.520(7) Å α=90° β= 90° γ=90°	a = 9.8322(2) Å b = 9.8322(2) Å c = 47.9529(10) Å α=90° β=90° γ=120°
Volume [$Å^3$]	2186.49 (14)	6020.9 (3)	3037.38(17)	5605.0(12)	4014.64(14)
Z	4	8	4	8	6
D_{calc} [Mg/m^3]	1.256	1.147	1.311	1.165	1.244
μ [mm^{-1}]	0.083	0.604	0.158	0.672	0.176
F(000)	896	2240	488	2128	1620
Crystal size [mm^3]	0.6 x 0.4 x 0.3	0.3 x 0.2 x 0.05	0.2 x 0.2 x 0.2	0.3 x 0.1 x 0.04	0.4 x 0.3 x 0.2

Θ range	2.14° to 25.8°	2.96° to 71.06°	2.94° to 28.66°	3.57° to 70.87°	2.93 to 28.63°
Index ranges	$-17 \le h \le 17$, $-16 \le k \le 16$, $-14 \le l \le 14$	$-33 \le h \le 33$, $-21 \le k \le 19$, $-14 \le l \le 15$	$-12 \le h \le 15$, $-19 \le k \le 20$, $-23 \le l \le 23$	$-15 \le h \le 16$, $-6 \le k \le 10$, $-59 \le l \le 58$	$-15 \le h \le 14$, $-16 \le k \le 16$, $-26 \le l \le 28$
Refl. collected	14589	88345	25560	33602	29066
Independent reflections	4030 [R(int)=0.0276]	5797 [R(int) = 0.0533]	7206 [R(int)=0.0577]	5244 [R(int) = 0.0504]	13803 [R(int) = 0.0588]
Completeness [%] to Θ	99.8 (Θ 25.2°)	100 (Θ 67.7°)	99.80 (Θ 26.31°)	99.6 (Θ 67.7°)	99.8 (Θ 26.3°)
Absorption correction	Multi-scan	Multi-scan	Multi-scan	Multi-scan	Multi-scan
Max. and min. transmission	0.638 and 1.000	0.592 to 1.000	0.664 and 1.000	0.845 to 1.000	0.733 and 1.000
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/ restraints/parameters	4030 / 2 / 282	5797 / 14 / 375	7206 / 0 / 391	5244 / 0 / 328	13803 / 0 / 759
GooF on F2	1.042	1.062	1.006	1.049	1.000
Final R indices [I>2sigma(I)]	R1= 0.0446, wR2= 0.1170	R1= 0.0590, wR2= 0.1572	R1= 0.0588, wR2= 0.1363	R1= 0.0467, wR2= 0.1189	R1= 0.0552, wR2= 0.1113
R indices (all data)	R1= 0.0446, wR2= 0.1171	R1= 0.0652, wR2= 0.1631	R1= 0.0897, wR2= 0.1551	R1= 0.0527, wR2= 0.1246	R1= 0.0794, wR2= 0.1279
$\Delta\rho_{max}$, $\Delta\rho_{min}$ [e·Å^{-3}]	0.24 and -0.18	0.39 and -0.37	0.68 and -0.38	0.36 and -0.27	0.325 and -0.281

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